# POTENTIAL PSYCHOTOMIMETICS: BROMOMETHOXYAMPHETAMINES AND STRUCTURAL CONGENERS OF LYSERGIC ACID

by

David Earl Nichols

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Pharmacy in the Graduate College of The University of Iowa

May, 1973

Thesis supervisor: Associate Professor Charles F. Barfknecht

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

---

PH.D. THESIS

---

This is to certify that the Ph.D. thesis of

David Earl Nichols

has been approved by the Examining Committee for the thesis requirement for the Ph.D. degree in the College of Pharmacy (Medicinal Chemistry) at the May, 1973 graduation.

Thesis committee: C F Beyerstein
Thesis supervisor

J F Long
Member

Carl T. Carrico
Member

R. V. Smith
Member

J Rocca
Member

DEDICATION

To Maxine and Chuck

## ACKNOWLEDGEMENTS

The author gratefully acknowledges the financial support provided by the National Defense Education Act Fellowship. The author expresses his appreciation to Dr. Charles F. Barfknecht for extending the privilege of working on this problem and for his encouragement and endless enthusiasm during the course of this work.

The author expresses his sincere gratitude to the staff and faculty members, and to fellow graduate students in the College of Pharmacy for the encouragement and many suggestions given during the course of this work.

TABLE OF CONTENTS

TABLE OF CONTENTS, continued

# LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES, continued

# INTRODUCTION

Certain novel highly active compounds which produce specific and dramatic psychic alterations have been classified as psychotomimetics. Terms such as hallucinogens, phantastica, eidetics, psychodysleptics, and psychedelics have also been suggested (1), depending on which aspect of the effects is given priority.

Psychotomimetics have been defined (2,3,4) as substances which produce changes in thought, perception, and mood, occurring alone or in conjunction with each other, without causing major disturbances of the autonomic nervous system. High doses generally elicit hallucinations. Disorientation, memory disturbance, hyperexcitation, or stupor and even narcosis occur only when excess dosages are administered and are thus not characteristic. Included in this classification are many natural drugs and decoctions which have been discovered and used throughout man's history.

Until recently drugs of this type were obtained from extracts of plants and natural substances, but advances in chemistry have led to the isolation and identification of many of the active principles, and in addition have led to

the development of totally new synthetic agents. A number of recent reviews concerning psychotomimetics have appeared (5-12).

Scientific inquiry into the nature of action of psychotomimetics may prove fruitful in several areas. First, and of primary concern, is the widely held belief that the study of psychotomimetics and chemically-induced psychosis may give insight into the nature of mental illness, and in particular schizophrenia. While it is no longer generally believed that the psychotomimetics can produce model laboratory psychoses, the fact that profound effects are exerted on mental functioning by chemical agents such as these lends credence to the idea that certain types of mental illness are the result of chemical imbalances or of endogenous toxins acting in areas of the brain which are critical for normal behavior. Second, psychotomimetics may be helpful in understanding consciousness, brain functioning, and perhaps also certain aspects of human behavior. Unfortunately, many of the features which make these drugs useful for such studies have also made them one of the classes of most widely abused drugs by contemporary society, especially the young.

There are at least three general types of psychotomimetics (13):

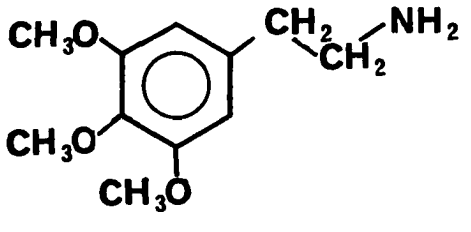
1. Substituted indolealkylamines, including LSD (d-lysergic acid diethylamide), psilocin, psilocybin, and substituted tryptamines.

2. Substituted phenethylamines, including mescaline (3,4,5-trimethoxy-β-phenethylamine), "STP" (DOM; 2,5-dimethoxy-4-methylphenylisopropylamine), and various ring-substituted phenylisopropylamines (amphetamines).

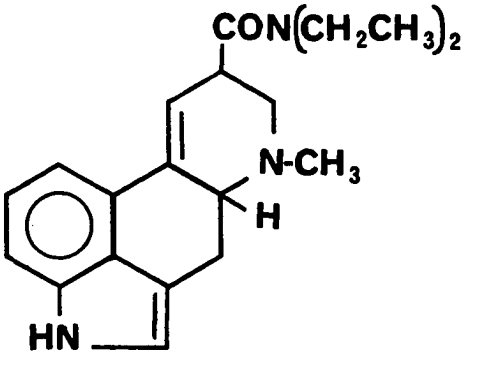
3. Miscellaneous, including tetrahydrocannabinol (THC), myristicin, phenyclidine, cholinolytic drugs such as Ditran$^{R}$, and others.

The latter category encompasses many distinct types of chemical species. Since the psychotomimetic effects of some of these are merely toxic side effects and do not delineate their pharmacological spectrum of activity, this discussion will deal with only those compounds comprising the first two divisions.

L. Lewin rediscovered for the western world the small cactus Lophophora williamsii in 1888, and drew attention to its hallucinogenic properties (14). Eight years later Arthur Heffter isolated three alkaloids from this cactus, including mescaline 1 (15) and in 1919 Späth synthesized this material and established its chemical structure as




1




2

3,4,5-trimethoxy-β-phenethylamine (16). However, more recent interest in such mind altering drugs probably began with the discovery of the effects of d-lysergic acid diethylamide (LSD) 2.

The following is a portion of the translation of the verbatim account of Hofmann following his accidental ingestion of a minute amount of LSD during routine laboratory manipulations:

> On a Friday afternoon, April 16th, 1943, while working in the laboratory, I was seized by a peculiar sensation of vertigo and restlessness. Objects, as well as the shape of my associates in the laboratory, appeared to undergo optical changes. I was unable to concentrate on my work. In a dreamlike state, I left for home, where an irresistible urge to lie down and sleep overcame me. Light was so intense as to be unpleasant. I drew the curtains and immediately fell into a peculiar state of "drunkenness," characterized by an exaggerated imagination. With my eyes closed, fantastic pictures of extraordinary plasticity and intensive color seemed to surge towards me. After two hours, this state gradually subsided and I was able to eat dinner with a good appetite. (17)

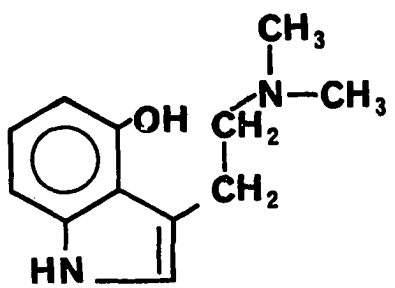
Although LSD is the most potent psychotomimetic which has been reported, its chemical complexity precludes the synthesis of many analogs which might be useful in determining which portions of the molecule are responsible for its behavioral effects. It is therefore desirable to attempt to simplify portions of the LSD molecule, to study the pharmacology of these individual "fragments," and then to

attempt to extrapolate to the molecule as a whole. Fortunately, LSD is not completely unique in its action and a discussion of the inter-relationships between LSD and certain other psychotomimetic agents will be helpful.

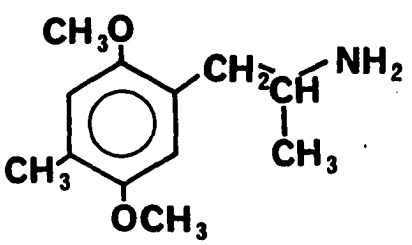
Both the subjective impressions of the hallucinatory effects of compounds derived from lysergic acid, tryptamine, and phenethylamine, and the demonstration of cross-tolerance between LSD, psilocybin, and mescaline imply a common mechanism for their action (18).

Karreman, Isenberg, and Szent-Györgyi have proposed an electronic or "submolecular" hypothesis for the actions of psychotropic drugs (19). Calculations by these workers of various electronic parameters for several molecules, including LSD, led them to conclude that such drugs as chlorpromazine, LSD and serotonin were potent electron donors. Snyder and Merril (20) and Kang and Green (21) have performed similar calculations for a series of psychotomimetic phenethylamine derivatives and substituted indolealkylamines, including LSD. Good correlation was found between the energy of the highest occupied molecular orbital (HOMO) and psychotomimetic potency and it was proposed that the correlative data suggest a common mode of action for these hallucinogens at a hypothetical receptor.

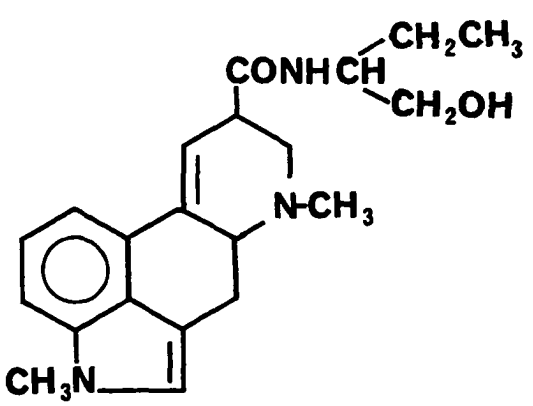
Martin and Eades (22) have produced data which suggest that the mode of action of LSD-like psychotomimetics is similar to that of tryptamine and is different from that of serotonin (5-hydroxytryptamine; 5-HT) or 5-hydroxytryptophan. They studied the effect of LSD, mescaline, psilocin 3, DOM 4, methysergide 5, and tryptamine in facilitation of the flexor reflex and in evoking the stepping reflex in the chronic spinal dog. Their findings are consistent with the hypothesis that LSD, psilocin, mescaline, DOM, and methylsergide have a similar type of agonistic activity and mode of action.




3




4




5

Meek and Fuxe (23) have also presented data which show that N,N-dimethyltryptamine (DMT), DOM, LSD, and psilocybin all have the ability directly to stimulate 5-HT receptors, and suggest that this may be related to the hallucinogenic effect.

Van Vunakis, et al,(24) have produced d-lysergic acid antibodies in rabbit and guinea pigs and have developed a radioimmunoassay for the hapten. LSD and several related ergot alkaloids were potent competitors for the antibody site. DMT, 4-hydroxytryptamine, and mescaline were only about ten times less effective than lysergic acid itself. The suggestion was made by these workers that the antibody receptor site recognizes structural features resembling the LSD molecule, in particular the aromatic nucleus and the ethylamine side chain.

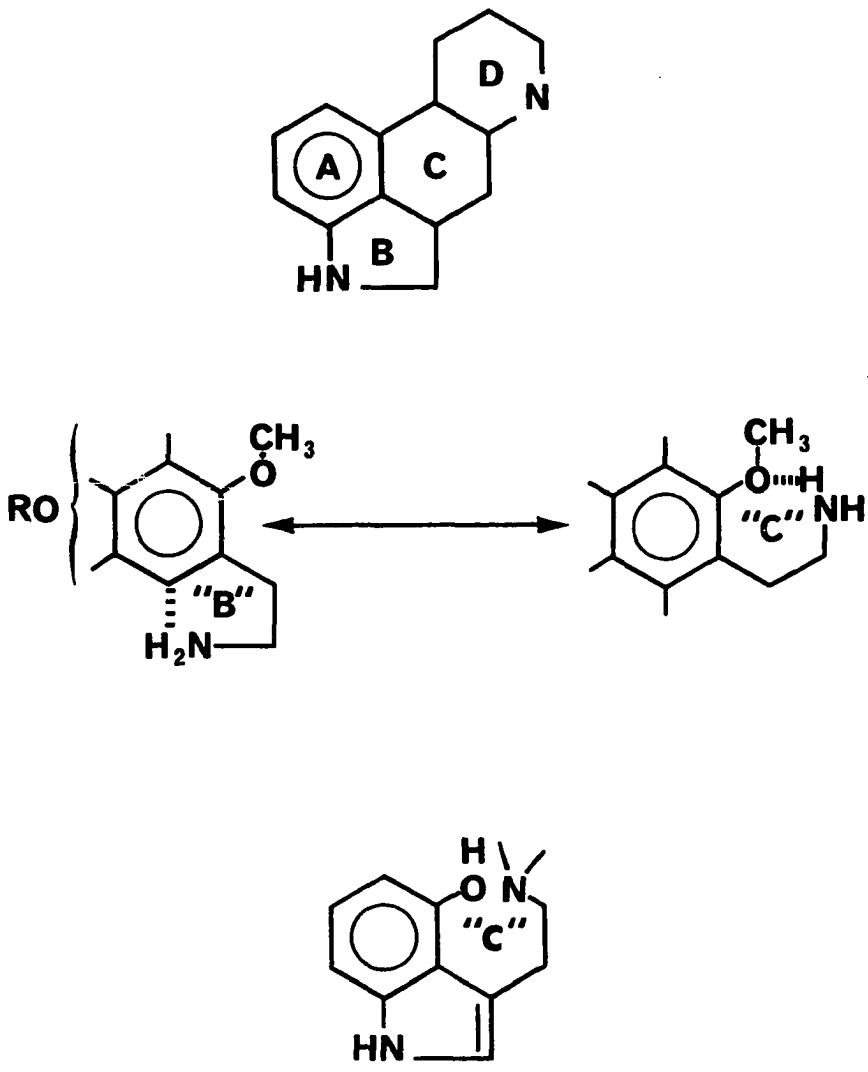
Although these studies do not prove that the indole-alkylamine and phenethylamine psychotomimetics interact at the same receptor or receptor system, they at least lend support to the theory and lay a basis for considering molecules which are structurally simpler than LSD as models of psychotomimetic agents in general.

Snyder and Richelson (25), apparently assuming LSD to have an ideal conformation, have attempted to show that psilocin and methoxylated phenethylamine derivatives fulfill certain steric requirements which allow them to assume

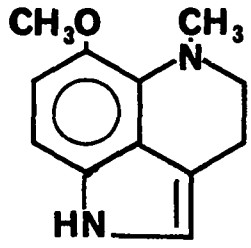
conformations resembling the B and C rings of LSD by intramolecular hydrogen bonding (Figure 1). They suggest that the phenethylamine derivatives, in addition to being able to assume a conformation resembling the C ring of LSD by hydrogen bonding between the amine N-H and the ortho methoxyls, can also approximate the B ring by hydrogen bonding between the N-H and the pi cloud of the aromatic nucleus. The former concept seems tenable, that is, that hydrogen bonding can occur to an ortho methoxyl; however, the possibility of hydrogen bonding to the aromatic pi electrons has been disputed (21,26,27). Recent data by Cooper and Walters also tends to refute this concept (28).

Chothia and Pauling (27) have considered probable conformations for several hallucinogenic molecules and have correlated these conformations with each other and with those of nerve transmitter molecules. In using this approach they have considered interatomic distances, relative bond directions, and torsion angles, based on crystallographic data. They show that the structure of LSD is fairly rigid, and that phenethylamine and tryptamine derivatives contain a planar group and a flexible side chain which can assume several different conformations whose energies are not widely separated. They conclude that there are the following correlations between these conformations and that of LSD: 1.) a charged nitrogen atom 510-570 picometers from

FIGURE 1. CONFORMATIONS OF PHENETHYLAMINES AND TRYPTAMINES RESEMBLING THE B AND C RINGS OF LSD, AS PROPOSED BY SNYDER AND RICHELSON (25)



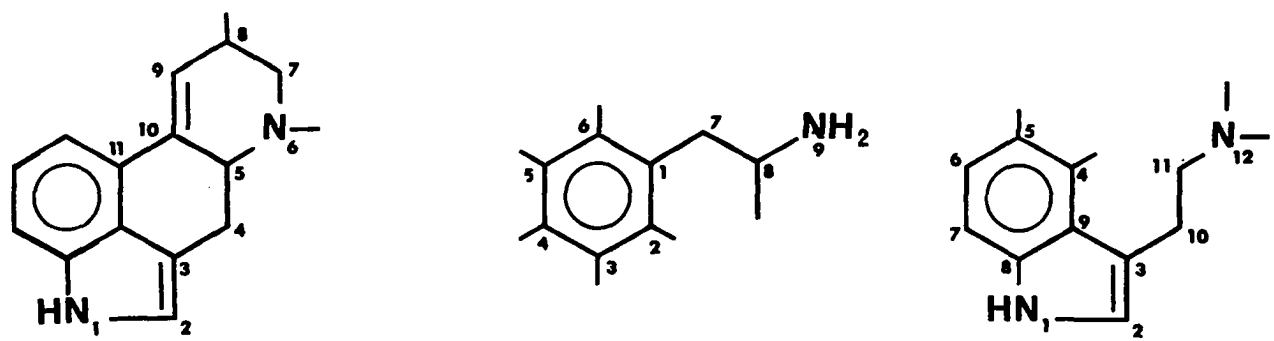
the center and 70-140 picometers above the plane of an aromatic ring; 2.) a nitrogen or oxygen atom corresponding to position 5 in phenethylamine derivatives; and usually, 3.) a point of electron density corresponding to the 9,10-double bond in LSD, the 4 oxygen atom in tryptamine derivatives, or the 2 oxygen atom in phenethylamine derivatives. They note that although it appears possible for the nitrogen atom to form a hydrogen bond to an oxygen atom at the 2 position in phenethylamine derivatives and to the 4 position in tryptamines, as proposed by Snyder and Richelson (25), the conformational correlation with LSD is higher when these bonds are not formed. Some importance may be attached to correlate 3. This is supported by observations that 9,10-dihydro LSD is inactive (29), that an ortho methoxyl greatly enhances activity in the methoxylated amphetamines (30), and that the placing of a 4-hydroxyl or methoxyl on dimethyltryptamine (DMT) results in a five-fold increase in activity, as well as rendering the compound orally active (DMT is active parenterally only). In addition, Lee, et al,(31) have prepared O-methyl nordehydrobufotenin 6 and found it to be active. Although it does not satisfy correlate 1 of Chothia and Pauling, it has the required aromatic system and point of electron density at the 4 indole position.




6

Since amphetamines and tryptamines have freely rotating alkylamine groups whose energy barrier to rotation is small, preferred conformations of the free molecules are not necessarily the same as those of the molecules upon interaction with the receptor. Whereas Chothia and Pauling (27) based their correlations on crystallographic data, Kang and Green (21) have carried out analyses to determine which stereochemical characteristics are common to the three classes of compounds, and have described conformations which most closely resemble the conformation of LSD. In these conformations the phenyl groups of the amphetamines and the tryptamines correspond to ring A of LSD. The N-6 nitrogen of LSD corresponds to the N-9 of the amphetamines and to the N-12 of the tryptamines (Figure 2). Interatomic distances between comparable carbons and nitrogens $D_{C11-N6}$ of LSD, $D_{C1-N9}$ of amphetamines, and $D_{C4-N12}$ of tryptamines are all about 3.6 Å. This model suggests that the necessary conditions for hallucinogenic activity are the aromatic character

FIGURE 2. CONFORMATIONS OF PHENETHYLAMINES AND TRYPTAMINES RESEMBLING LSD AS PROPOSED BY KANG AND GREEN (21)



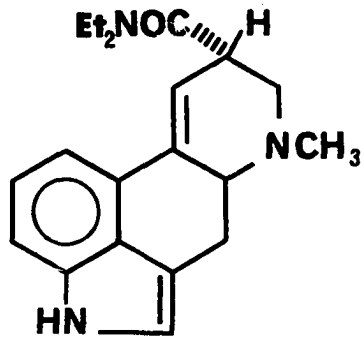
of ring A and an amino group in a position like N-6 of LSD. In this study, Kang and Green further propose that the pyrrole moiety and the hydroxyls, and the methoxyls, of the tryptamines and amphetamines, respectively, serve the role of conferring a high HOMO on the system. Kang and Green note that structures which have a fixed geometry, such as 2-amino-1,2,3,4-tetrahydronaphthalenes, may be more potent compounds than the freely rotating analogs.

Molecular models suggest that, in LSD, N-6 is near or below the aromatic plane. When the N-methyl assumes the equatorial position, the lone pair electrons of N-6 are directed below the plane of the system. If N-6 is a site for interaction with the receptor or a portion of it, this result would suggest that interaction occurs on the lower face of the LSD molecule.

If the findings of Chothia and Pauling (27) and of Kang and Green (21) are combined, two general requirements are suggested which must be met for maximal activity: 1.) points of high electron density corresponding to the 2 and 5 positions of the amphetamines, the indole nitrogen and 4 position of the tryptamines, and to the 9,10-double bond of LSD, which at least serve to activate the aromatic nucleus; 2.) an aliphatic amino function about 3.6 Å from the aromatic nucleus and lying approximately in the plane of the aromatic ring in a conformation which places it in a position

correlating with N-6 of LSD. It seems likely that these essential elements may reflect points of attachment or binding to some receptor surface.

A structural feature unique to LSD and not considered in the above correlations is the diethylamide function at C-8. An examination of molecular models shows that in LSD the diethylamide function is equatorial, lying approximately in the plane of the molecule, whereas in iso-LSD 7 it is



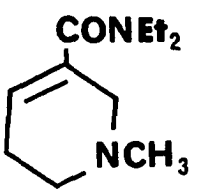

7

axial and protrudes downward. If the receptor does indeed interact with the bottom face of LSD, steric interference from a bulky axial substituent at this position might preclude the possibility of such interaction. However, steric factors are probably not the sole explanation for the importance of this group. It has been shown that small changes in substitution on the amide nitrogen produce, in every instance, a molecule with decreased activity when compared with the diethyl substitution (10). Compounds with similar

substituents such as the pyrrolidyl or piperidyl amide have all been found to be less active than LSD. It is difficult to account for this loss of activity and no satisfactory explanation has been offered in the literature.

It is tempting to speculate that LSD may bind at two separate receptors, one for the aromatic ethylamine portion, and a second for interaction with the diethylamide moiety. Such a two-receptor interaction might account for the complexity of biological effects induced by LSD.

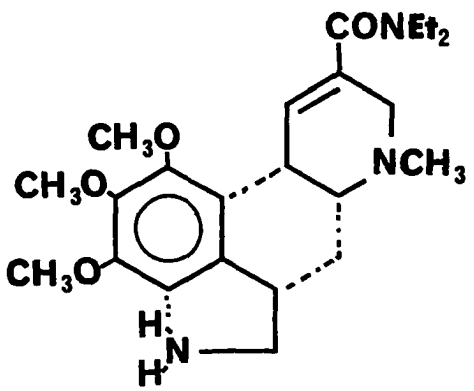
Data which may support such an hypothesis were recently reported by Smythies, et al,(32) who treated rats with 1-methyl-1,2,5,6-tetrahydropyridine-3-diethylcarboxamide (THPC) 8. Doses of THPC which displayed no behavioral effects alone markedly potentiated the effects of a subsequently administered dose of mescaline, but showed an antagonistic effect toward the action of LSD. Smythies, et al, (32) interpreted this result to indicate that the "psychotomimetic receptor" might be shaped to accommodate the




8

structure of LSD, and that mescaline only mimicked the indole portion of LSD, whereas with THPC both the "top" and "bottom" halves of the receptor site were now filled (Figure 3). This author feels that a two-receptor hypothesis to

FIGURE 3 INTERACTION OF THPC AND MESCALINE AT AN LSD RECEPTOR AS PROPOSED BY SMYTHIES, ET AL (32)




explain the action of psychotomimetics is a more rational approach, rather than making the assumption that a single receptor accepts two active moieties at the same receptor site. Findings by Cooper and Walters (28) which will be discussed later are also strong evidence to dispute the contention that phenethylamines can assume conformations which approximate the indole ring.

Although the double bond in THPC is conjugated with the amide carbonyl function, some analogy exists to the D ring of LSD. Leonard and Stonier (33) have conducted studies in an attempt to determine the biochemical nature of the THPC-mescaline interaction. They found that THPC in doses up to 100 mg/kg had no effect on gross behavior in mice or rats. Effects of mescaline, THPC, and combinations of mescaline plus THPC on brain levels of 5-HT and catecholamines were investigated. Combinations of mescaline and THPC did not affect whole brain levels of 5-HT, norepinephrine, or dopamine. THPC alone did increase significantly the depletion of 5-HT following blockade of its biosynthesis by pretreatment with p-chlorophenylalanine.

These investigators reported only two findings which suggest that THPC modifies the actions of mescaline. It was found that THPC can reverse the effect of mescaline in reserpinized mice which also have been treated with α-methyl-m-tyrosine (α-MMT), and that THPC in combination with mescaline potentiates the depletion of brain norepinephrine following administration of 4,α-dimethyl-m-tyramine (H77/77). The significance of these results to the THPC-mescaline interaction is unclear.

We have recently found (34) that THPC is inactive as a cholinergic agonist on isolated guinea pig ileum. However, a single perfused dose produces a strong contraction in

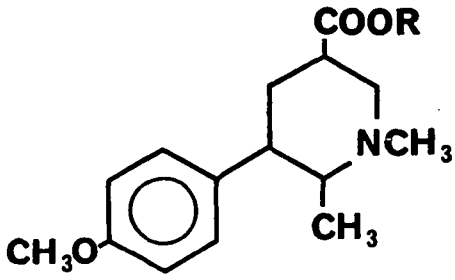
smooth muscle. It has not been determined if this contraction is mediated *via* α receptors or histamine receptors, but it is known that the contraction is not blocked by 5-HT antagonists.

If the D ring of LSD is considered to be a piperidine-3-carboxylic acid derivative, the study of such systems may aid in further examining the actions of LSD. This might be especially revealing if LSD does indeed interact at two distinct receptors. Although many analogs of piperidine-3-carboxylic acid have been prepared which resemble LSD in many respects (35), biological data is lacking for most of these.

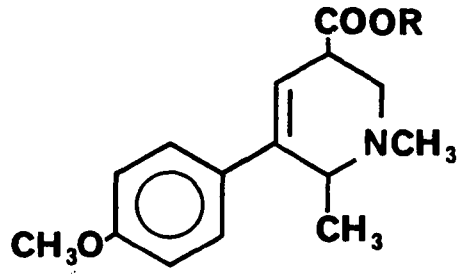
The diethylamide of cocaine has been found to be a longer-acting but more toxic local anesthetic than cocaine in mice. It was found specifically to antagonize the effects of serotonin on rat uterus, whereas cocaine inhibited both serotonin and oxytocin (36).

Plieninger (37) prepared 9 and 10 as analogs of lysergic acid. 9 Was reported to be oxytocic but 10, with the double bond in conjugation with the aromatic ring, had markedly greater potency.

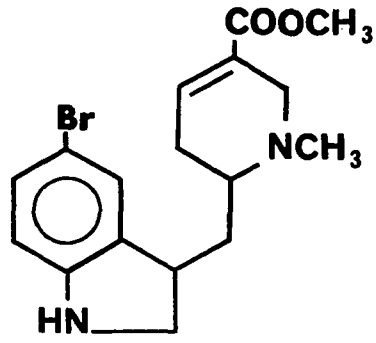
The dihydroindole derivative 11 was prepared by Sivajian and found to be 1/48 as active as LSD in studies with guinea pigs (38).




9



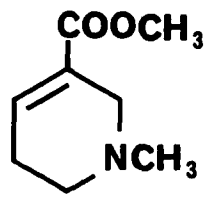

10



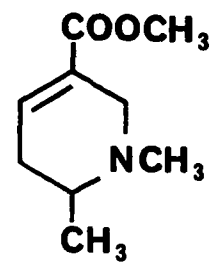

11

Sivajian (38) also reported biological activities in the guinea pig for arecoline 12, 6-methylarecoline 13, and 5-phenyl-6-methylarecoline 14. These compounds were devoid of LSD-like activity in guinea pigs.

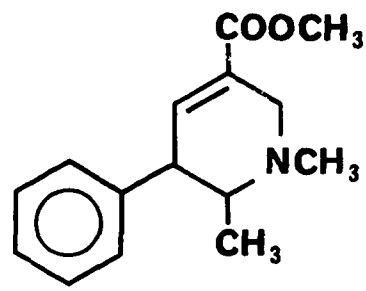
Pradhan and Dutta (39) have studied the effects of arecoline 12 on several behavioral schedules in rats. It usually decreased responses, especially at high doses, and was reported to cause an overall depression of motor activity. Based on antagonism studies with scopolamine,




12




13




14

methylscopolamine, and mecamylamine, they have concluded that arecoline appears to have a muscarinic cholinergic type of central depressant effect. Matilla, et al,(40) have also found that arecoline greatly reduced motor activity in mice, while causing analgesia. The activity of arecolinium ion has been determined by Burgen (41) to be 1.4 times that of carbachol on isolated guinea pig ileum.

Arecoline has been studied by Herz (42) and Herz and Yacoub (43), and has been shown to decrease the conditioned avoidance response in rats. In schizophrenic patients, Pfeiffer and Jenney (44) found that it increased emotional responses and body movements and that 0.5 mg s.c. plus 3 mg

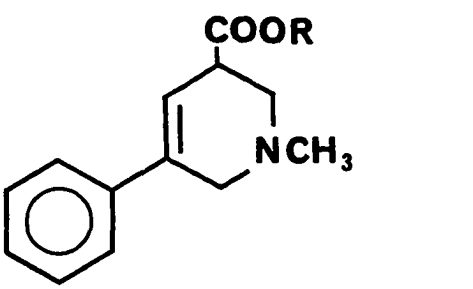
of methyl atropine produced a "lucid" period of 15-20 minutes in some patients. An extensive review on the pharmacology of arecoline has recently appeared (45).

In connection with these studies it is interesting to note that LSD and 2-bromo LSD (BOL) are potent inhibitors of serum or nonspecific cholinesterase *in vitro*, whereas they are less potent toward true cholinesterase (46). A concentration of $8 \times 10^{-6}$ molar LSD or BOL was found to produce 50% inhibition of serum cholinesterase *in vitro*. Pseudocholinesterase from a number of areas in human brain was inhibited 60% by $5 \times 10^{-6}$ molar LSD, a concentration which had no effect on true cholinesterase. However, Zsigmont, *et al*,(47) compared anticholinesterase activity of psilocybin, bufotenin, and 5-HT in human plasma, erythrocytes, and homogenates of gray matter and found no correlation between anticholinesterase activity *in vitro* and psychotomimetic effects of these compounds.

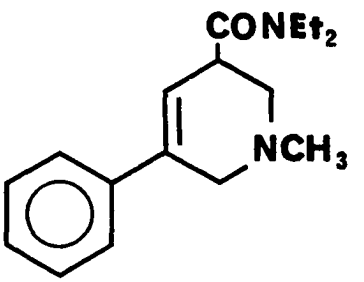
Lehrfield (48) prepared a series of 6-substituted nicotinic acid derivatives as analogs of lysergic acid, but no biological data were reported.

Hohenlohe-Ochringen, *et al*,(49) prepared 15 as an analog of lysergic acid. No activity for this compound was reported but it might be anticipated that it would be similar in action to compound 10, prepared by Plieninger (37).

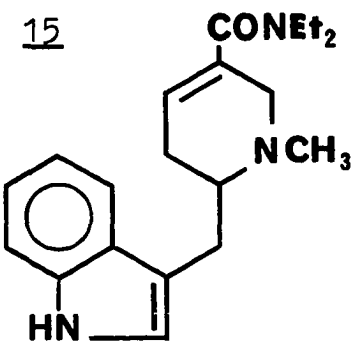
Julia, Igolen and Kolb (50) have prepared 16 and 17 as analogs of lysergic acid but no biological activities have been reported.




15

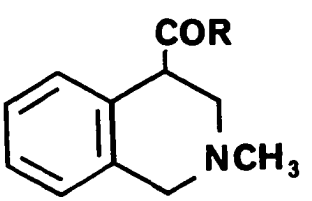



16




17

Derivatives of N-methyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid 18 have been prepared by Thuiller, et al,



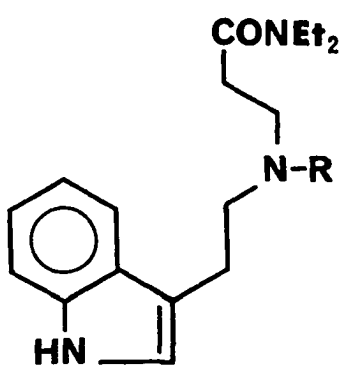

18 R = OH

19 R = $N(C_2H_5)_2$

(51) as D ring analogs of lysergic acid. No biological data were reported. Cheng, et al,(34) have found that the hydrochloride of the N,N-diethylamide 19 has no cholinergic, α-adrenergic, or 5-HT agonist activity in guinea pig ileum or smooth muscle tissue.

Smythies, et al,(52) have prepared even simpler D ring analogs. These workers prepared the diethylamides of simple aliphatic carboxylic acids and found that N,N-diethylbutyramide (DBA) partially antagonized the psychotomimetic effect of dimethyltryptamine in rats.

Sklar, et al,(53) found the diethylacrylamide adduct 20 to be approximately 1/10 as active as LSD in mice, although Norris and Blicke (54) reported 21 to have little oxytocic activity.




20 R = $C_2H_5$

21 R = $CH_3$

Thus it can be seen that systems resembling the D ring of LSD have been prepared, and that many of them show a high degree of potency. Hofmann (10) has noted that LSD itself was prepared as an analog of nikethamide, a well-know analeptic agent. While the structural analogies between LSD and some of these compounds are tenuous, the fact remains that many compounds resembling the LSD D ring have potent effects both in vivo and in vitro.

Having considered the D ring of LSD as a potentially active fragment, a more obvious portion of LSD is that of an indolealkylamine. Based on this structural feature, much early speculation was put forth regarding a possible effect of LSD on serotonin systems. Gaddum (55,56) established that LSD in concentrations as low as $10^{-9}$ g/l antagonizes the contracting effect of serotonin on smooth muscle tissue. Assuming that such antagonism also exists in the brain, Woolley and Shaw (57) advanced the hypothesis that the hallucinogenic effects of LSD are based on a relative serotonin deficiency in the brain. However, Curtis and Davis (58) have shown that in some tissues there may be no LSD-serotonin antagonism; in fact, there may even be a degree of synergism. It has been found that BOL is a more potent serotonin antagonist than LSD and that it crosses the blood brain barrier, yet it is non-hallucinogenic (59). It has even been

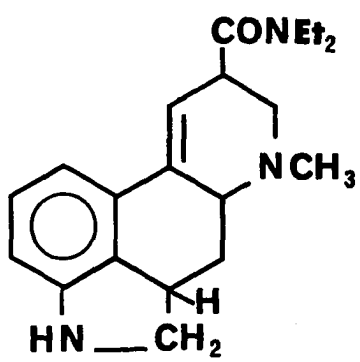
demonstrated that BOL can block the effects of LSD if administered in sufficient amounts prior to the ingestion of LSD (13).

LSD does exert many effects on central serotonin mechanisms. Freedman, et al,(60) have shown that LSD induces an increase in 5-HT concentration in the brain. Aghajanian, et al,(61,62) have linked activity of the midline raphe system with 5-HT metabolism, and have shown that LSD can diminish firing of those neurones (63). Giarman and colleagues (64,65) early emphasized that levels of 5-HT reflected the net result of a number of component processes, and a single effect such as antagonism is not likely to provide a satisfactory explanation. Indeed, it has been found that 5-HT antagonism and hallucinogenic potency in a series of lysergic acid derivatives could not be correlated (66). Thus Woolley and Shaw's original hypothesis (57) seems refuted, but it is not necessarily true that LSD's effects on central 5-HT are not a factor in the overall action of the drug. Aghajanian has treated this possibility in a recent review (67).

The question remains whether the indolealkylamine moiety can be considered as an essential element within the LSD molecule. Whereas a great number of substituted indolealkylamines (tryptamines in particular) are known to be highly active psychotomimetics (10,68) some evidence indicates that

an indole nucleus is not essential, and by deduction, the indolealkylamine moiety in LSD may not be the primary factor in determining activity.

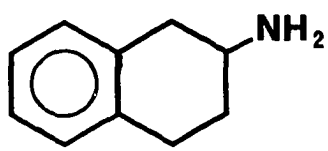
Analogs of lysergic acid have been prepared which include certain features of the LSD molecule but do not contain an indole nucleus. The most impressive finding in this regard is that of Gorodetzky and Isbell (69) who found that in human volunteers, 2,3-dihydro-LSD 22 possesses approximately one-sixth and one-eighth the potency of LSD in producing mydriasis and mental effects, respectively. It should be noted that the time of onset and peak activity was



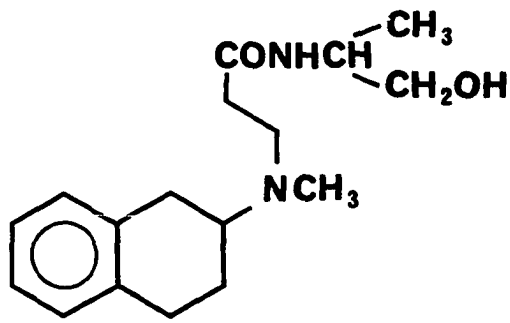

22

somewhat delayed from that of LSD, and the possibility of an *in vivo* aromatization process, or the generation of an active metabolite cannot be ruled out.

Marini-Bettolo, Chiavarelli, Bovet, and co-workers (70-80) have tested over 200 derivatives of 1,2,3,4-tetrahydro-2-naphthylamine (2-aminotetralin) 23. This system is analo-



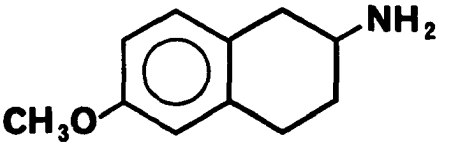

23



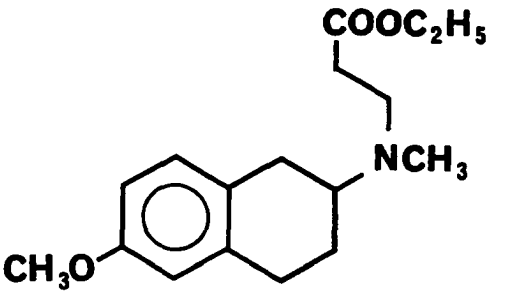

24

gous to lysergic acid with the B and D rings removed. One of the derivatives 24 bore a striking resemblance to ergonovine and was a potent oxytocic with little vasomotor action (73). From their study of derivatives of 23, Marini-Bettolo, et al,(70) and Bovet, et al,(80) concluded that the 1,2,3,4-tetrahydro-2-naphthylamine element, rather than the indole moiety, in the structure of the ergot alkaloids is essential for sympatholytic activity.

Kraushaar (81) has conducted similar studies with derivatives of 6-methoxy-1,2,3,4-tetrahydro-2-naphthylamine 25. Several of the compounds tested in Kraushaar's study had marked oxytocic activity on rabbit uterus, in vivo, as well as effects on blood pressure, respiration rate, and intestinal motility and tone. Compound 26 which bears an



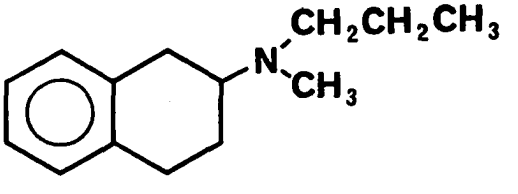

25




26

interesting similarity to lysergic acid, had little oxytocic activity when compared with the parent compound 25. Kraushaar wisely points out that a closer approximation to the structure of lysergic acid does not necessarily mean an increase in the intensity of the effect, since Rothlin (82) has already demonstrated that neither lysergic acid nor its simple amide have an effect on the uterus.

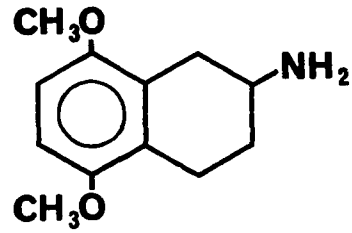
Pennefather and Thorp (83) found that N-methyl-N-propyl-2-aminotetralin 27 has high and specific antiserotonin activity at $10^{-7}$ molar, whereas the parent 23 was a 5-HT agonist.




27

Violland, et al,(84,85) have considered this approach in relation to the psychotomimetics and have prepared an extensive series of aminotetralins related to open chain methoxylated phenethylamine derivatives. Many of these compounds were active but produced sedation and analgesia rather than psychotomimetic effects. Most of the compounds were less active than mescaline in mice.

Barfknecht and co-workers (86,87) have studied the effects of 5,8-dimethoxy-2-aminotetralin (5,8-ADT) 28 in mice and rats. This compound was highly potent, but also possessed sedative rather than psychotomimetic activity in mice. However, symptoms such as piloerection and mydriasis, typical of sympathomimetic agents, were observed. In rats 28 had an amphetamine-like effect. The 5,8-dimethoxy substitution seems to have been a good choice since 5,8-ADT is

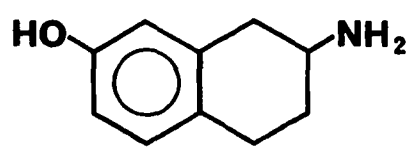



28

more potent by about a factor of ten than any of the compounds which were prepared by Violland, et al (84). Whereas Violland chose substitutions in the 6 and 7 positions,

5,8-ADT satisfies Chothia and Pauling's requirement (27) for points of electron density corresponding to the indole nitrogen and to the 9,10-double bond in LSD.

Green, et al,(88) have used total valence electron calculations to predict potential psychotomimetic activity for aminotetralin derivatives. To test their predictions, the electroencephalographic effects of three 2-aminotetralins (7-hydroxy, 7-methoxy, and 6-methoxy) were compared with mescaline, LSD, and amphetamine in normal rats and in rats made tolerant to mescaline. Based on their electronic calculations the most active compound was predicted to be the 7-hydroxy-2-aminotetralin 29. Cross-tolerance between 29 and mescaline was demonstrated in these studies and 29 appeared to have high potency.

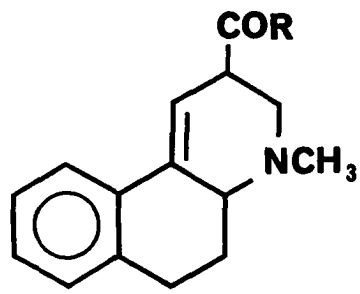



29

Voigtlander has also prepared aminotetralin derivatives as analogs of lysergic acid (89).

Horii, et al,(90) have synthesized 2-carboxy-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline 30a lacking only the indole nucleus. These workers claimed patents on

derivatives of this compound as uterine contracting agents whose potency was on the order of 1/15-1/16 that of ergonovine.




30a R = OH

30b R = $N(C_2H_5)_2$

Although no gross behavioral effects have been reported for several of these compounds it should be noted that none contain an indole nucleus, yet many are reported to retain a high degree of pharmacological activity. It would thus appear that the significance of the indole moiety is questionable.

This leads to consideration of another possible structural element incorporated into LSD which may account for its activity. Brodie, et al,(91) have pointed out that, in addition to its indole structure, LSD possesses a phenethylamine skeleton. These workers suggested that its main action involves stimulation of central adrenergic receptors.

This contention was reiterated by Costa, et al,(92) in 1962, and would seem to be in agreement with previously discussed correlations.

The close structural relationship between catecholamines and the psychotomimetic phenethylamines suggests some effect of these compounds on adrenergic systems. Based on cross tolerance studies and other correlative data, LSD might have a similar action. Previously mentioned 2,3-dihydro-LSD 22 could be considered as a phenethylamine from the 4 indole position, whereas it no longer fulfills the requirements of an indolealkylamine.

Clemente and Lynch (93) have presented evidence which demonstrates the α-agonist activity of mescaline in various peripheral tissues. Mescaline also possesses α-blocking properties in some tissues, produces only slight β-stimulatory action, and does not stimulate cholinergic receptors.

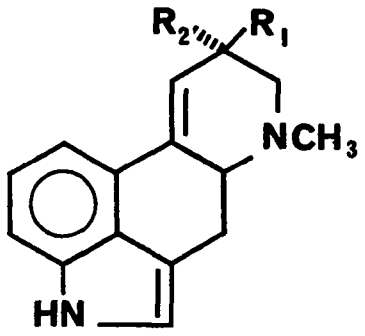
Several studies have been made to determine the effects of α and β blocking agents on the actions of LSD. Matussek and Halback (94) found that pretreatment with ergotamine, an α-blocker, prior to LSD administration resulted in intensification of the LSD syndrome. Dixon (95) has studied the effect of phenoxybenzamine and dibenamine, α-blockers, on LSD-induced aberrant behavior (LSD-AB) and locomotor excitation in rats. Dibenamine produced a clear inhibition of both types of activity only in high doses, whereas

phenoxybenzamine was particularly effective in producing a profound inhibition of LSD-AB and locomotor activity in all doses tested. The effects of the β-blocking agents pronethalol and propranolol were also studied. Both agents produced an inhibition of LSD-AB while leaving locomotor activity unimpaired.

Dixon (95) and Resnick, et al,(96) have shown that pretreatment with reserpine, an agent which depletes brain stores of norepinephrine and serotonin, markedly accentuates the behavioral effects of LSD. However, Dixon (95) showed that pretreatment with para-chlorophenylalanine, an agent which inhibits serotonin biosynthesis in the brain without influencing brain levels of catecholamines, had no influence on either LSD-AB or on locomotor excitation. In contrast, a single dose of α-methyl-p-tyrosine, a potent inhibitor of catecholamine synthesis in the brain without effect on cerebral serotonin concentrations, produced a strong inhibition of LSD-AB and, to a lesser extent, locomotor activity. In the same study disulfiram, a compound which inhibits the conversion of dopamine to norepinephrine, produced only a small attenuation of LSD-AB. After disulfiram pretreatment brain levels of norepinephrine, but not those of dopamine, are reduced. Dixon suggests that the persistence of aberrant behavior points to a dopamine-mediated effect. Goldstein (97) however, has noted that disulfiram does not

completely inhibit brain norepinephrine synthesis, and thus the possibility exists that in Dixon's study a sufficient reduction of this catecholamine may not have been achieved.

Woodruff, et al,(98) have studied antagonism by lysergic acid derivatives to the effect of dopamine on Helix neurones. In the brain of the snail, Helix aspersa, there are identifiable neurones which are hyperpolarized and inhibited by dopamine. From a study of the structural requirements for dopamine-like activity in the brain of Helix, it was concluded that the action of dopamine on these cells is mediated via specific dopamine receptors (99). In Woodruff's study (98) LSD was found to be a powerful antagonist of the dopamine response in Helix. The hyperpolarization produced by dopamine is completely abolished by 0.01 μmole of LSD. The dopamine antagonism produced by LSD was usually not reversible by washing the preparation for thirty minutes. This action was not necessarily related to the ability of LSD to block 5-HT, since the neurones used in the study are depolarized by 5-HT, but are hyperpolarized by dopamine. Furthermore, although LSD blocks the actions of both 5-HT and dopamine on these neurones, the antagonism to 5-HT is readily reversed by washing, whereas the dopamine block is persistent. Ergonovine 31 is also a potent dopamine antagonist in Helix. However, the isomer 32 was shown to have no dopamine blocking activity. It should be noted that 31 is a




31 $R_1$ = $CONHCH(CH_3)CH_2OH$

$R_2$ = H

32 $R_1$ = H

$R_2$ = $CONHCH(CH_3)CH_2OH$

derivative of lysergic acid, whereas 32 is a derivative of isolysergic acid. The diethylamide of isolysergic acid (iso-LSD) is inactive as a psychotomimetic (17).

In the studies described above the implication is made that LSD-induced behavioral changes may be due primarily to a catecholamine-mediated effect. It is interesting to note that the phenothiazine and butyrophenone type tranquilizers are commonly used to abort a "bad LSD trip." These drugs markedly accelerate turnover of dopamine in the corpus striatum (100,101). The mechanism is thought to be a blockade of dopamine receptors, causing enhancement of a postulated feedback to presynaptic dopamine neurones, which respond by increased dopamine synthesis.

Dopamine may also be involved in the action of other psychotomimetics. For example, Dill (102) has shown that dopamine is an effective inhibitor of the dyskinesias produced by intrastriatal injection of mescaline in rats. Haloperidol, a potent dopamine blocker, was found to reduce significantly the mescaline response in this study.

Without making conclusions as to mechanism of action, it seems that substantial evidence exists supporting the contention of a catecholamine-mediated effect of LSD on behavior. Other psychotomimetics may have a similar mode of action and numerous studies have produced results consistent with this possibility.

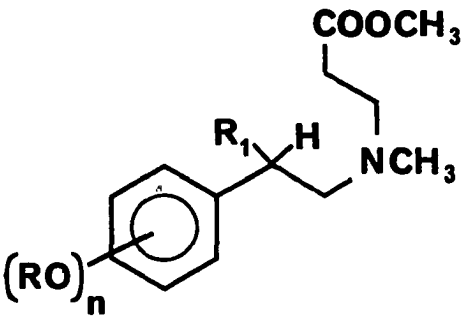
It is interesting that dopamine should be implicated as a catecholamine involved in the action of psychotomimetics, since it has recently been postulated by Snyder (103) that a dopaminergic mechanism may be responsible for schizophrenia. He suggests that involvement of norepinephrine modifies the effect to give a paranoid type of schizophrenia. Snyder proposes that development of a drug that would stimulate dopamine but not norepinephrine mechanisms in the brain might produce a "pure" model of schizophrenia. Although this suggestion is certainly open to criticism, certain features of the action of amphetamine have been linked primarily with dopaminergic mechanisms in the brain. The striking similarity (104) of amphetamine-induced psychosis

to paranoid schizophrenia suggests that these conditions might have a common mechanism of action. Faurbye (105) regards the acute paranoid psychosis resulting from chronic abuse of amphetamines as the paradigm of certain forms of schizophrenia.

Angrist (106) and Angrist, et al,(107) have experimentally induced amphetamine psychosis in man by chronic administration of (+), (±), or (-) amphetamine. No significant difference was found between cumulative doses of (+) or (-) amphetamine required to induce psychosis. These workers suggested, based on the observations of Snyder, et al,(108-110) that amphetamine psychosis is mediated via a dopaminergic pathway. It was found in a study with one individual, that while the cumulative dosage of (+) or (-) amphetamine required to induce psychosis did not differ significantly, olfactory delusions, hallucinations, loss of insight, associated fear, and terror were most intense after administration of the (-) isomer of amphetamine (106). Much evidence has been presented which tends to confirm that such effects are most consistent with a dopamine mediated mechanism (103, 108-110). Hanson (111) has also found that L-DOPA potentiates the action of amphetamine and it has been noted that some patients receiving L-DOPA therapy for Parkinson's disease manifest psychotic symptoms (112).

It seems plausible that a phenethylamine feature in LSD could be responsible for at least some of the behavioral effects, and further examination of such systems may provide additional evidence to support this hypothesis.

Baltzly and co-workers (113,114) found that esters 33 and 34 exhibited significant oxytocic activity when the



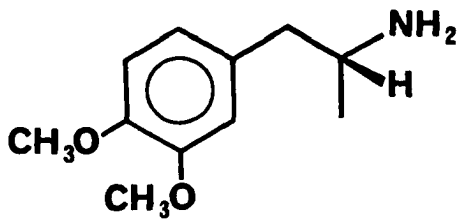

33 $R_1$ = H

34 $R_1$ = OH

rings contained methoxyl substituents. The potency was approximately five to ten percent that of ergonovine. This compares favorably with other oxytocic analogs of lysergic acid, such as the tricyclic systems prepared by Horii, et al,(90) mentioned earlier. The diethylamide 30b, certainly resembles the structure of ergonovine to a greater extent than do 33 or 34, yet it is less active.

It is well known that the various stereoisomers of LSD are inactive (10), with the exception of the isomer having the 5R,8R absolute configuration (115,116). Levo-LSD is

inactive even in doses as high as ten milligrams (117). It will be noted that the amphetamines have a center of asymmetry and thus have two possible enantiomers. Barfknecht and Nichols (118) have tested the two enantiomers of 3,4-dimethoxyamphetamine (3,4-DMA), a compound which is inactive in humans but approximately twice as active as mescaline in rats. Based on stereochemical considerations, they propose that the R-(-) isomer 35, due to its similarity to the phen-




35

ethylamine structure in LSD, may be responsible for psychotomimetic activity. In testing however, neither isomer was able to reproduce the psychotomimetic effect in rats. Surprisingly, a combination of the R-(-) isomer with (+) amphetamine, a "quasi-racemate," reproduced the effects of racemic 3,4-DMA. The suggestion was made, based on these observations, that both enantiomers may be required for psychotomimetic activity.

Shulgin, however, has found that the (-) isomer of STP (DOM) is the active enantiomer in man (119), and Benington, et al,(120) have found that the (-) isomers are responsible for the effects of DOM and 2,5-dimethoxy-4-bromoamphetamine (121,122) (DOB) in the rat.

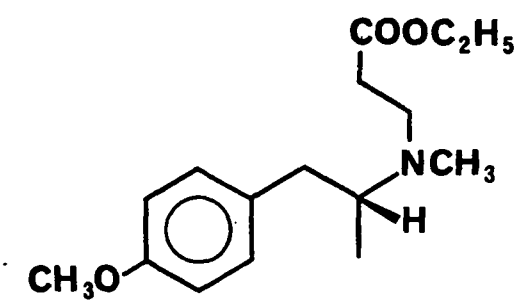
Generally optical isomers of a drug molecule possess differing degrees of biological activity. In the case of amphetamine, norepinephrine uptake into synaptosomes from noradrenergic regions of the brain is inhibited to a greater extent by the S-(+) than by the R-(-) isomer (123,124).

Morgan, et al,(125) have found that in the rat norepinephrine levels in the telencephalon were 35% lower after treatment with (+)-N-methylamphetamine. The (-) isomer had no such effect. Hendley and Snyder (126) have shown that in rabbit vas deferens and iris muscle, where norepinephrine is the predominant catecholamine, a marked preference is shown for (+) amphetamine. In rabbit retina, where dopamine is the chief catecholamine, no stereoselectivity was found for (+) or (-) amphetamine. Beckett and Al-Sarraj (127) have found that the two isomers of amphetamine are not equally good substrates for side chain metabolizing enzymes in certain animal species.

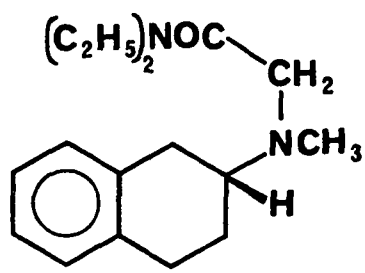
Other studies which further elaborate the biological response differences between stereoisomers of active compounds abound in the literature, but the work by Pfeiffer

(128) is particularly interesting and has been referred to as "Pfeiffer's Rule." Pfeiffer found positive correlation between the isomeric ratio of activity and the human dose in milligrams for a series of compounds, and showed that the lower the effective dose for a given racemic compound, the greater the difference between the potency of the isomers. Since Gordis (129) has found that no racemization of either isomer occurs when amphetamine is administered to man, one might anticipate that study of the stereoisomers of psychotomimetic amphetamines would prove interesting.

Although LSD only recently has been considered as a phenethylamine (21,27,118) this approach was used in earlier literature in relation to oxytocic activity of other lysergic acid alkaloids (37,113,114). Plieninger (37) resolved N-methyl-p-methoxyamphetamine and studied the oxytocic activity of the ethyl acrylate adducts. He found the levoisomer 36 to be more potent than the dextro. Marini-Bettolo



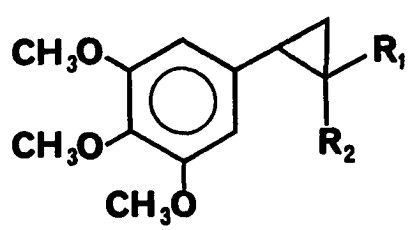

36




37

and co-workers (70) resolved the 2-aminotetralin derivative 37 and found that the dextro isomer possessed the lysergic acid-like activity. Although the signs of rotation were reported for 36 and 37, the absolute configurations were unknown at that time. More recent studies have shown that the phenylisopropylamines possess the R-(-) and the 2-aminotetralins possess the R-(+) absolute configuration (130, 131). Thus both 36 and 37 have the R configuration and correlate with lysergic acid. Although these agents have arisen from a search for better oxytocic agents, one may speculate that they reflect the action of the lysergic acid nucleus itself.

Cooper and Walters (28), alluded to earlier, have tested 38 and 39 for psychotomimetic activity in mice and




38 $R_1 = NH_2$; $R_2 = H$

39 $R_1 = H$; $R_2 = NH_2$

rats. Their studies revealed that 38, which was about twice as active as mescaline, was four to eight times more active than the cisoid isomer 39. These data are in agreement with

the above discussion and support the view that psychotomimetic phenethylamines interact with the receptor in a transoid conformation.

Based on all the previously cited studies it does not seem unreasonable to suggest that the simplest structural element in LSD which might be responsible for activity is that of a phenethylamine. (In this view aminotetralins are considered to be rigid phenethylamines.) In the Chothia and Pauling study (27) it was noted that a correlation was drawn between the indole nitrogen and the 5-methoxyl of the phenethylamine derivatives, thus suggesting that one requisite for psychotomimetic activity was a point of higher electron density, as supplied by the non-bonded electrons at this position. As implied by the calculations of Snyder and Merril (20), the pyrrole ring, as incorporated into the indole nucleus, serves to activate the aromatic system. It is possible then that the indole nucleus only serves the role of a highly-activated aromatic system, completely analogous to a methoxylated phenethylamine derivative. This rationale is also advanced by Kang and Green (21). The phenethylamine analogy would suggest interaction with catecholamine systems.

Inconsistencies are apparent however, if one assumes that the action of LSD is mediated solely via a catecholamine mechanism, and indeed experimental evidence tends to

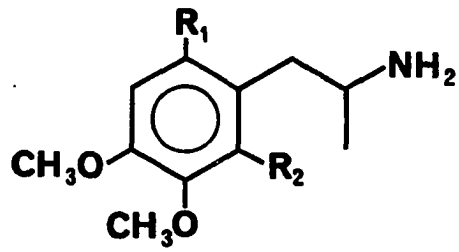
show that LSD has effects on many systems. Based on the activities of several systems related to LSD and discussed previously, the following hypothesis is advanced; that the activity of LSD may be approximated and its effects studied by consideration of a dual action of a highly activated phenethylamine and of a nicotinamide or β-alanine derivative, either of the latter two corresponding to the D ring of LSD. The phenethylamine derivative should possess the R-(-) absolute configuration to correspond to the stereochemistry of LSD. This hypothesis suggests that psychotomimetic activity results from interaction with at least two receptor systems or neural pathways in the brain. It seems likely that one of these is dopamine mediated; the other(s) probably involve stimulation of either 5-HT or α-receptors. Such a dual hypothesis would not be unusual, since cross relationships have been demonstrated between other neural systems, in particular between cholinergic and dopaminergic mechanisms in striatal neurons (102,132-135), and between cholinergic systems and turnover of 5-HT and dopamine (136).

Extensive work has been done on methoxylated phenethylamine psychotomimetics, and certain structure-activity relationships have been proposed. Consideration of the actions of the phenethylamine type psychotomimetics may give insight into the action of LSD. In the following pages, parameters

such as distribution, metabolism, and correlations of activity with various physical and chemical properties will be considered.

Gessner and Page (137) have presented data regarding the chloroform-water partition coefficients of several tryptamine derivatives and of LSD; higher lipid solubility tended to be correlated with higher activity. However, no such study of lipid solubility for the various methoxylated amphetamines appears to have been done, although Hendley and Snyder (138) have remarked that changes in the positions of the methoxyl groupings do not seem to cause any marked alteration in physical properties such as lipid solubility. No data have been presented to support this view. It has been a subjective observation in this laboratory in preparing certain analogs of psychotomimetic amphetamines, that some of them appear less water soluble than others; hence, the implication of differing lipid solubilities is made. Based on studies of rate of urinary excretion, Snyder, et al, (139) have suggested that DOM may be slowly absorbed into the circulation. Parallel studies have not been conducted with other compounds.

Mitoma (140) has studied the distribution and metabolism of two amphetamine derivatives, 2,4,5-trimethoxyamphetamine (TMA-2) 40 and 2,3,4-trimethoxyamphetamine (TMA-3) 41. TMA-2 is highly active as a psychotomimetic in man whereas




40 $R_1 = OCH_3$; $R_2 = H$

41 $R_1 = H$; $R_2 = OCH_3$

the latter compound is essentially inactive (141). Using 14-C labelled compounds it was shown that TMA-3 concentrations are higher in the brain than are those of TMA-2, during the period studied. It was concluded that the amount of drug that enters the brain is not the sole factor that determines psychotomimetic potency. In vitro studies with rat and rabbit liver homogenates indicated that TMA compounds were metabolized primarily by O-demethylation. There appeared to be no correlation between the rate of metabolism and the activities of the compounds studied.

Sargent, et al,(142) studied the metabolism by O-demethylation of 3,4-dimethoxyphenethylamine (DMPEA) using 14-C labelled methoxyls at the 3 or 4 positions. Their findings showed that the rate of conversion of the 4-methyl group to $14\text{-}CO_2$ by rats in vivo was approximately fifteen times that of the 3-methyl. Based on these results and the work of Schweitzer and Friedhoff (143), Sargent's group suggested that 4-methylation may also be an important metabolic

pathway for the catecholamines, in addition to the previously established 3-methylation reaction (144). Musacchio and Goldstein (145) have studied the O-demethylation of N-acetyl mescaline in rats. Demethylation at the 4 position accounted for 53% of the O-demethylated products and 5-demethylation, for 28%.

Hendley and Snyder (138) studied the inhibitory action of methoxylated amphetamines on normetanephrine uptake by brain slices. These authors reported a close correlation between psychotomimetic potency and ability to inhibit normetanephrine uptake. TMA-2, DOM, and 2,4,6-trimethoxyamphetamine exhibited five to seven times greater affinity for the normetanephrine transport system than did normetanephrine itself. In contrast, 3,4,5-trimethoxyamphetamine (TMA), 2,3,5-trimethoxyamphetamine, and TMA-3 were considerably less potent uptake inhibitors. This correlation suggests that the sites of normetanephrine uptake may be related in some way to the locus of action of these drugs. Hendley and Snyder suggest that a likely site may be the post-synaptic receptors for norepinephrine.

Kang and Green (145) have calculated values for the energy of the highest occupied molecular orbital (HOMO; $E_H$) for a series of methoxylated amphetamines. Using the intermediate neglect of differential overlap (INDO) method, and standard bond lengths and angles, they subjected the results

to a stepwise multiple regression analysis and derived an equation which related the equimolar hallucinogenic potency to the $E_H$:

$$\text{Log activity} = 18.7 + 35.1\ E_H \quad (p < 0.005)$$

Their correlation suggests that the ease of perturbability of the pi electrons of the amphetamines may be a determinant of hallucinogenic activity. These authors suggest that the amphetamines may form a low energy, reversible, pi-molecular complex with the brain receptor that somehow gives rise to hallucinations. Some of the compounds which were studied did not fit the correlation and it would be surprising if many other factors were not involved in the mechanism of action.

Antun, et al,(147) have shown a correlation between the native fluorescence of a series of methoxylated amphetamines and their potency in humans. The fluorescence of a molecule is also related to the electronic states of the system and DOM, which had the highest $E_H$ as determined by Kang and Green (146), also had the highest degree of fluorescence.

Bailey and Verner (148) have measured molar absorptivity and $\lambda_{max}$ in the ultraviolet for the $\pi$-$\pi^*$ transition, or local excitation band, of a series of eight methoxylated amphetamines. Log potency was well correlated ($p < 0.01$) with both $\lambda_{max}$ and molar absorptivity. The lower energy and increased probability of occurrence for this transition

appear to correlate positively with hallucinogenic potency ($p < 0.01$) ($\lambda_{max}$ correlates with $\epsilon$ for this series). The results offer supporting evidence for formation of a low energy reversible pi-molecular complex of the amphetamines with some brain receptor, as discussed above.

Sung and Parker (149), using an NMR method described by Foster (150), have determined the association constants for pi-molecular complexes of a series of fifteen methoxylated amphetamines with 1,4-dinitrobenzene. Calculations were based on changes in chemical shift for the 1,4-dinitrobenzene protons (acceptor protons) with and without various concentrations of donor molecules (amphetamines). Their data show that mono and di-methoxylated amphetamines have donor strength about equal to N,N-dimethylaniline and to the phenothiazines, respectively. The trimethoxyamphetamines are even stronger complexing agents. A significant correlation was found between K, the association constant, and potency ($p < 0.03$, if 3,4-DMA, TMA-3, and TMA were excluded from the correlation. This is consistent with certain anomalies also noted by Antun, et al,(147) and by Bailey and Verner (148).) This correlation also implies that molecular complex formation may be one of the important factors for hallucinogenic activity.

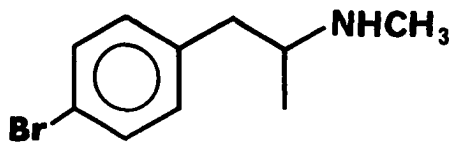
Shulgin, et al,(30) have published a comprehensive structure-activity relationship study for an extensive series of one-ring psychotomimetics. These workers studied the clinical effects of members of the series and reached some general conclusions: 1.) length of chain; in no case was there a decrease in activity with the introduction of an α-methyl group on the phenethylamine skeleton, while there seems to be a decrease by further extending the chain to four carbon atoms; 2.) location of methoxyl substituents: ortho- in no case was the psychotomimetic activity decreased, and in most cases there was a substantial increase resulting from this addition; meta- with three exceptions m-methoxylation decreased the activity; para- most active compounds were substituted in the para position. Animal studies have shown that para substitution is by itself sufficient for psychotomimetic activity (151), whereas these data show that it is not mandatory for human activity. Replacement of the p-methoxyl function of TMA-2 38 with a p-methyl results in a five-fold increase in potency: 3.) nature of the substituents; transformation of two adjacent methoxyl groups into a methylenedioxy ring, with one exception, led to no loss of potency, and a noteworthy increase was observed in several cases. Replacement of the p-methoxyl with an ethoxyl does not result in loss of activity, whereas, if placed in either the 2 or 5 positions there is

a loss of activity. It appears that a substituent at the 4 position affords stability and immunity from metabolic attack.

Smythies, et al,(151) tested a series of tri-, di-, and monomethoxyamphetamines in the rat. Their results indicated that the essential feature of the "hallucinogenic" molecule in the series tested was the p-methoxy group. Para-methoxyamphetamine (PMA) was the most potent compound tested. Beaton, et al,(152) tested p-chloro, p-fluoro, and p-methylamphetamine. Of the three, p-methyl was least active, producing only stimulant effects. All animals injected with either p-chloro- or p-fluoroamphetamine died.

The ethyl homolog of DOM has been prepared recently and tested (153,154). This compound, 2,5-dimethoxy-4-ethylamphetamine (DOEt) was shown to be approximately twice as active as DOM in man. It was contrasted with DOM however, in that it produced "feelings of enhanced self-awareness in the complete absence of hallucinogenic or psychotomimetic effects."

Knoll (155) has tested meta and para substituted derivatives of N-methylamphetamine which show the same spectrum of activity in rabbit, cat, and rat as does LSD. Para-bromo-N-methylamphetamine 42 (V-111) produced effects which closely resemble the action of LSD in rats and possessed about 1/10 the potency of LSD but had a longer duration of



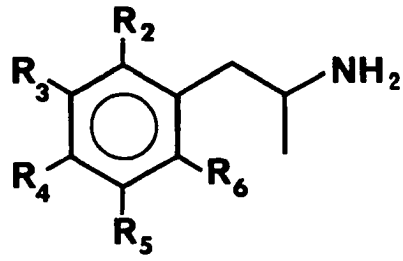

42

action. V-111 was also found to decrease the sensitivity of the CNS to psychotomimetic agents. This effect was produced by daily administration of V-111 for six months. Three months after discontinuing the drug, only 34% of the treated rats had regained normal sensitivity to the drug. At the end of six months 84% had regained sensitivity. Based on an extensive series of substituted N-methylamphetamines which were tested, Knoll concluded that proper substitutions, mainly in the para position, give the molecule the character of an LSD-type psychotomimetic in animal experiments. These data support the concept that the para substituent is important for activity.

# STATEMENT OF THE PROBLEM

## Part I. Proposed Synthesis of Certain Bromomethoxyamphetamines

In studying phenethylamines as models for the action of LSD, it would be useful to examine further various parameters involved in activity. It has been suggested that a primary mode of metabolism for the methoxylated amphetamines is O-demethylation, and probably at the para position. In DOM, a compound for which the possibility of para-O-demethylation does not exist, it has been found that the major metabolic fate in rats is oxidation of the para-methyl to $CH_2OH$ (156). It was felt that placing inert atoms at the 4 position might prolong biological life in the body by affording stability to metabolic attack. The halogens seemed likely candidates for this role and accordingly it was decided to prepare the bromomethoxy compounds 43a-f. Bromine was selected for several reasons. The most obvious is the ease of preparation of bromo compounds over the other halogen homologs. The van der Waals radius of 1.95 Å for bromine as compared with 2.0 Å for a methyl (157) would minimize steric factors involved in comparison of 43f with DOM. It is also felt that the different electronic character of bromine will affect HOMO values and it may be



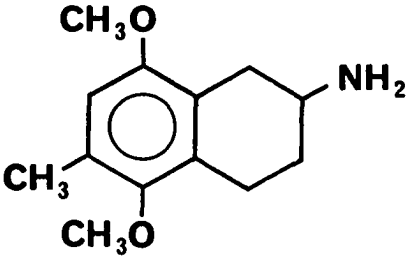

| Compound | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|
| 43a | Br | H | H | $OCH_3$ | H |
| 43b | H | Br | $OCH_3$ | H | H |
| 43c | H | $OCH_3$ | Br | H | H |
| 43d | Br | H | $OCH_3$ | $OCH_3$ | H |
| 43e | H | $OCH_3$ | Br | $OCH_3$ | H |
| 43f | $OCH_3$ | H | Br | $OCH_3$ | H |

possible to access the relative importance of metabolic stability versus high HOMO. Cassels (158) has cited unpublished work by other workers who showed that a bromine is nearly indistinguishable from a methoxyl in a simple Hückel LCAO-MO approximation. Johnson and Green (159) have performed CNDO total-electron calculations for a series of chloromethoxyamphetamines with the same substitution patterns as 43a-f. While the HOMO values reported (Appendix A) differ in absolute value from those of the proposed bromomethoxy compounds, one should be able to predict which substitution would be most active.

It was proposed to test compounds 43a-f for an effect on the conditioned avoidance response in rats as a preliminary screen for psychotomimetic activity (160). In addition to the preparation and testing of 43a-f it was also proposed to attempt the resolution of representative methoxylated amphetamines into their enantiomers for testing.

## Part II. Proposed Synthesis of 2-Amino-5,8-Dimethoxy-6-Methyl-1,2,3,4-Tetrahydronaphthalene as an LSD AC-Ring Congener

Structure 44 was proposed for synthesis since it represents a rigid analog of DOM. It was felt that if the

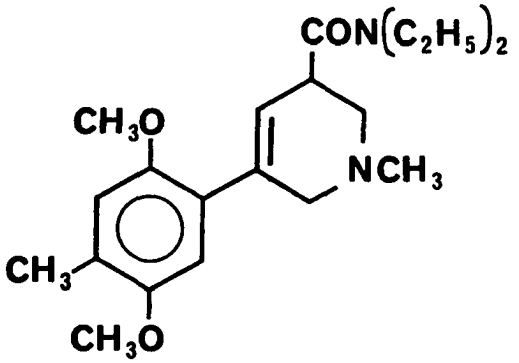



44

aminotetralin fragment in lysergic acid is the moiety responsible for the activity of LSD, then the fixed conformation of 44 might possess increased activity over that of DOM.

## Part III. Proposed Synthesis of an LSD AD-Ring Congener

To study the importance of the D ring of LSD it was proposed to prepare 45. This system presumably would pos-




45

sess a high HOMO as conferred on the system by the 2,5-dimethoxy-4-methyl substitution and is a close analog of LSD. Molecular models show that the two rings can lie in a nearly planar conformation. It will be noted that the tetrahydropyridine ring lacks the 6-methyl which was incorporated into Plieninger's compound 10, and thus resembles more closely Hohenlohe-Ochringen's system 15. In the amphetamines it is believed that the α-methyl group confers resistance to degradation by monoamine oxidase. It was felt that this protection was unnecessary in 45. In addition, no stereoisomers would exist and the des-methyl compound might

have higher potency than a racemic mixture in which only one enantiomer was in the proper conformation for receptor interaction.

# DISCUSSION

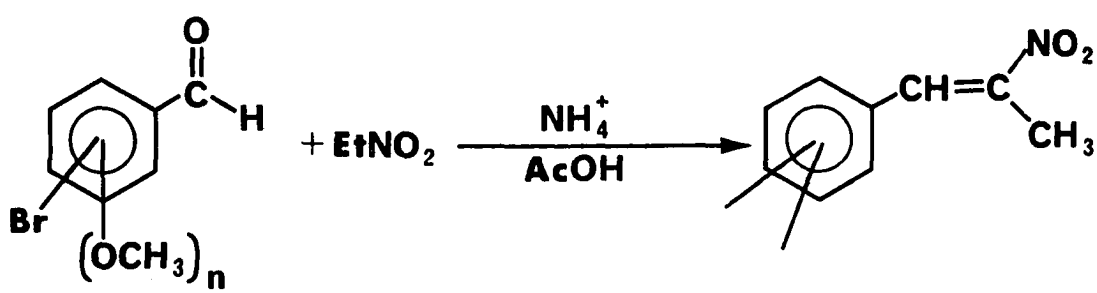
## Part I. Approaches to the Synthesis of Bromomethoxyamphetamines and the Asymmetric Synthesis of Amphetamine Enantiomers

Numerous bromomethoxy-β-phenethylamines have been reported in the literature. Most have been prepared as intermediates in the synthesis of complex alkaloids and have not been examined for activity. Synthesis of these compounds has been carried out in several ways. Many have been prepared by elemental bromination of ring methoxylated phenethylamines (161-164). The disadvantage of this approach is that the position taken by the bromine is based on well known rules for electrophilic substitution into aromatic rings, and substituent patterns are thus restricted.

In other cases bromomethoxy phenethylamines have been prepared by Zinc-HCl reduction (165-167), electrolytic reduction (168,169), or by catalytic reduction (170) of appropriate bromomethoxy precursors. For a general series of compounds it seemed most feasible to prepare suitably substituted bromomethoxy intermediates, followed finally by reduction to the amine. A route which has wide applicability is the lithium aluminum hydride (LAH) reduction of

β-nitrostyrenes (171-174). The method is general, but for the work described here it suffers from a major disadvantage in that aromatic bromine may be displaced by the powerful hydride ion, resulting in loss of halogen in the product (175,176). Erne and Ramirez (176) have reported that dehalogenation can be minimized when an aromatic bromine is present by using stoichiometric amounts of LAH.

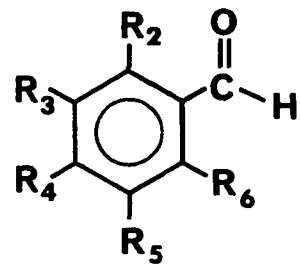
It was found that the extent of debromination could be reduced by conducting the LAH reduction at low temperatures (174) and using stoichiometric quantities of the reducing agent. Although yields were only in the range 30-40% using this technique it was felt that this was acceptable since the precursors were prepared in a fairly straightforward manner. The general synthetic scheme is outlined below.




46a-f 47a-f


47a-f 43a-f

The synthesis of the desired compounds was dependent on availability of the properly substituted benzaldehydes. With two exceptions, the aldehydes had been reported in the literature. The aldehyde substitutions for 46a-f are shown below. Aldehydes 46e and 46f are previously unreported.




| Compound | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|
| 46a | Br | H | H | $OCH_3$ | H |
| 46b | H | Br | $OCH_3$ | H | H |
| 46c | H | $OCH_3$ | Br | H | H |
| 46d | Br | H | $OCH_3$ | $OCH_3$ | H |
| 46e | H | $OCH_3$ | Br | $OCH_3$ | H |
| 46f | $OCH_3$ | H | Br | $OCH_3$ | H |

Elemental bromination in carbon tetrachloride of p-anisaldehyde by the method of Gray, et al,(177) gave 46b. Elemental bromination of veratraldehyde or 2,5-dimethoxy benzaldehyde in methylene chloride using anhydrous stannic chloride catalyst gave 46d and 46f, respectively. Preparation of 46a was accomplished by elemental bromination of

3-hydroxybenzaldehyde, followed by O-methylation. It has been reported by Pandya and co-workers (178) that bromination of 3-hydroxybenzaldehyde gave bromo substitution at the 4 position. However, substitution *para* to the hydroxyl was the only product isolated. This was confirmed by degradation of 46a to the corresponding benzoic acid and comparison of the melting point with the reported literature value. Confusion in the literature has probably resulted from the fact that the isomeric aldehydes 46a and 46c have the same melting points, as do their hydroxy analogs (179). However, the melting points of the corresponding benzoic acids differ considerably and comparison of the melting point with the reported values for the isomeric acids, prepared by unequivocal routes, confirmed proper identities. Substitution of the bromine into the 4 position of 46f was confirmed by nmr spectroscopy and by chemical degradation to the known 2,5-dimethoxy-4-bromobenzoic acid.

Preparation of 46c and 46e was accomplished by $LiAlH(O\text{-}t\text{-}Bu)_3$ reduction of the corresponding acid chlorides according to the method of Ho, *et al* (180). Surprisingly, 3-methoxy-4-bromobenzoic acid, the precursor for 46c, could be prepared by elemental bromination of 3-hydroxybenzoic acid in acetic acid (179), followed by O-methylation. This substitution is to be contrasted with that obtained by bromination of 3-hydroxybenzaldehyde, as discussed above.

The precursor for 46e, 3,5-dimethoxy-4-bromobenzoic acid, was prepared by di-O-methylation of commercially available 3,5-dihydroxy-4-bromobenzoic acid.

All α-methyl-β-nitrostyrenes 47a-f were conveniently prepared by condensation of the appropriate benzaldehydes with nitroethane in acetic acid containing ammonium acetate (181). In some cases no condensation initially occurred and the difficulty was traced to the presence of residual moisture in the aldehydes which had been air dried before use. This problem was avoided by thoroughly drying the aldehydes. The inhibitory effect of water on the aldehyde-nitroalkane condensation has been thoroughly studied by Crowell and Bell (182).

The α-methyl-β-nitrostyrenes were reduced using stoichiometric amounts of LAH and conducting the initial addition of the nitrocompounds to the reducing agent at solid-$CO_2$-acetone bath temperatures. Reduction mixtures were then allowed to warm to room temperature and were worked up in the usual way. Using this procedure yields were somewhat lower than could be desired, but dehalogenation was minimized. This was evident, for instance, in the case of the preparation of 43d. The amine hydrochloride as isolated required only one recrystallization to achieve analytical purity, whereas if debromination occurs the reduction

products have wide melting ranges and require multiple recrystallizations to increase and sharpen the melting point and give analytically pure material.

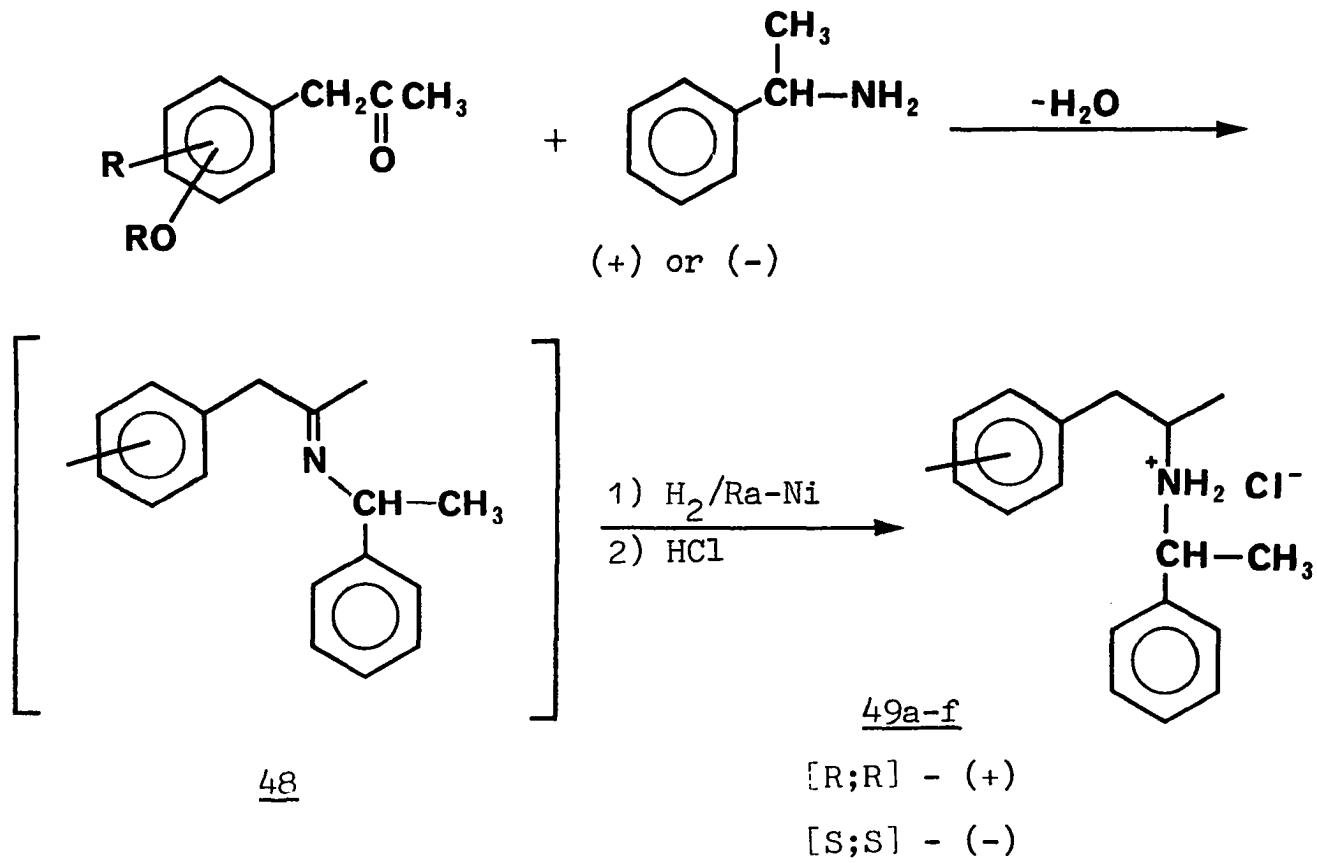
Compounds 43a-f were screened for an effect on the conditioned avoidance response in rats (183). The results of this screen have been published (121) and are given in Appendix B. The data presented is consistent with the hypothesis that the para substituent is important in conferring metabolic stability on the molecule, since only compounds having a para-bromine had mescaline-like activity.

During the preparation of the bromomethoxy amphetamines a number of known methoxylated amphetamines were prepared for comparison in behavioral testing. It was observed that certain of these methoxylated compounds possessed fluorescence under long-wave ultraviolet. It was subsequently found that there appeared to be a correlation between potency and intensity of fluorescence. It was decided to determine if a similar correlation existed for the bromomethoxy compounds and native fluorescence of 43a-f was investigated. Maxima for excitation and emission were determined for $2.91 \times 10^{-5}$ molar solutions of the compounds in water. This data, with the detailed procedure, has been reported (147) and is listed in Appendix C. A correlation between fluorescence and potency in rats could not be demonstrated in this case.

Methods for resolving methoxylated amphetamines have been used in this laboratory which utilized recrystallization of the diastereomeric amine di-(p-tolyl)-, or dibenzoyl-, (+) or (-) tartarates. This procedure is tedious and affords only poor yields. For example, attempts to resolve 2,5-dimethoxyamphetamine with dibenzoyl-(+)-tartaric acid, after a material loss of 85%, gave amine with an enantiomeric purity of only about 74%. In addition, derivatives of unnatural (-)-tartaric acid are expensive and it is therefore somewhat more costly to obtain substantial quantities of both isomers of the desired amine. It has been reported to us that nitrotartaranilic acids are excellent resolving agents for the amphetamines (184). However, before work based on a physical resolution was begun, a report was published in the literature describing the stereospecific synthesis of 3,4-dimethoxyamphetamine as an intermediate in the synthesis of (+) or (-) α-methyldopamine (185).

This author has improved this approach to provide a convenient source of enantiomerically pure amphetamines with varying substitution patterns. The route is represented in Figure 4. In the original method, the initial reductive step was accomplished at 100 atm pressure, and final hydrogenolysis was carried out using substantial quantities of

FIGURE 4. SCHEME FOR THE ASYMMETRIC SYNTHESIS OF AMPHETAMINE ENANTIOMERS



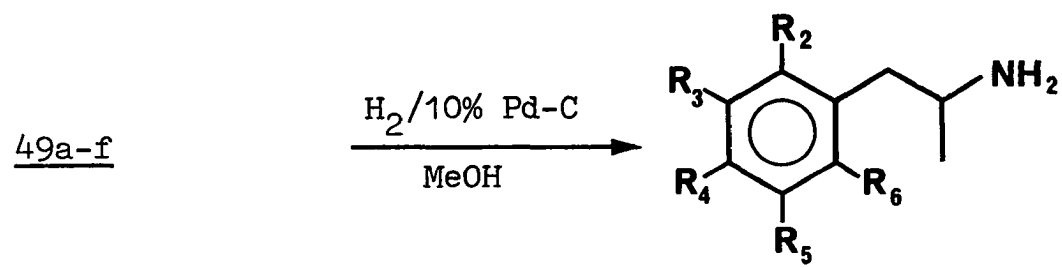

48

49a-f

[R;R] - (+)

[S;S] - (-)

FIGURE 4. (Continued)



reduced palladium chloride. The high pressure and catalyst expense involved in these two steps were considered the major disadvantages. The reported overall yield was also very poor. Preforming the imines 48 by refluxing the phenylacetones with α-methylbenzylamine in benzene with continuous water removal greatly improved yields and allowed facile reduction at 50 psig to the N-(α-phenethyl)-phenylisopropylamines 49a-49f. Hydrogenolysis of 49a-f was accomplished in quantitative yield utilizing 10% palladium on carbon, a less expensive reagent. In addition, the time for reaction completion was reduced, probably due to the higher surface area of the Pd-charcoal catalyst as compared with reduced palladium chloride. Amine enantiomers 50a-f were prepared to demonstrate the utility of the method (186, 187). The (+) and (-) isomers of 43f were also prepared by bromination of 50e and 50f following the method of Harley-Mason (163).

| Compound | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Isomer |
|---|---|---|---|---|---|---|
| 50a | H | H | H | H | H | (-) |
| 50b | H | $OCH_3$ | $OCH_3$ | H | H | (+) |
| 50c | $OCH_3$ | $OCH_3$ | H | H | H | (+) |
| 50d | $OCH_3$ | $OCH_3$ | H | H | H | (-) |
| 50e | $OCH_3$ | H | H | $OCH_3$ | H | (+) |
| 50f | $OCH_3$ | H | H | $OCH_3$ | H | (-) |

Analysis of enantiomeric purity of the isomers was accomplished by glc analysis of the α-methoxy-α-trifluoromethylphenylacetamides (MTPA amides). Dale, et al,(188) have used MTPA amides to determine absolute configuration and enantiomeric purity of amines by fluorine nmr. In the present work glc analysis was found to be more sensitive than the nmr method.

N-Trifluoroacetyl-S-prolylamides (TPC amides) (128, 189,190) of 50a-f were analyzed by glc for order of retention times. Westley, et al,(189) have pointed out in their studies that the SR diastereomeric TPC amide always elutes before the SS form. Although the stereospecificity of the asymmetric synthesis is strong presumptive evidence for predicting the absolute configuration of the enantiomers, the order of elution of the TPC amides confirmed that in every case the compounds which were prepared possessed the R-(-) and S-(+) configurations.

In collaboration with other workers, the general utility of this method has been demonstrated and the procedure has been used to prepare a large number of other methoxylated amphetamine enantiomers (187).

## Part II. The Synthesis of 2-Amino-5,8-Dimethoxy-6-Methyl-1,2,3,4-Tetrahydro-naphthalene and Discussion of the Route Used

Numerous methods have been reported for the preparation of 1,2,3,4-tetrahydro-2-naphthylamines. Violland, et al,(84,85) have recently surveyed the methods of major synthetic importance. It was evident from this survey that 44, the aminotetralin analog of DOM, could be prepared in a number of ways. First, the side chain could be added, functionalized, and then cyclized back into the ring in a manner similar to that reported by Zymalkowski and Dornhege (131). Two new approaches were examined briefly. The first is illustrated in Figure 5. The nitroester 56 was desired and it was anticipated that the ester function could be hydrolyzed and the resulting acid cyclized into the ring to give a 3-nitro-1-tetralone, which could be reduced to the desired compound. The sequence leading to the 3-carbomethoxy-2-nitropropiophenone 54 was straightforward and all steps proceeded in acceptable yields. However, as might be anticipated, the benzylic hydroxyl in 55 could not be selectively hydrogenolyzed in the presence of the aliphatic nitro group. Indeed, the nitro moiety proved to be more labile than the hydroxyl. Attempted catalytic reduction of 55 led to a mixture of 57 and 58, isolated as the hydrochlorides, and identified by broad absorption in the ir at 2800-3000 $cm^{-1}$

FIGURE 5. SCHEME FOR THE PREPARATION OF METHYL 3-NITRO-4(2,5-DIMETHOXY-4-METHYLPHENYL)-BUTYRATE 56

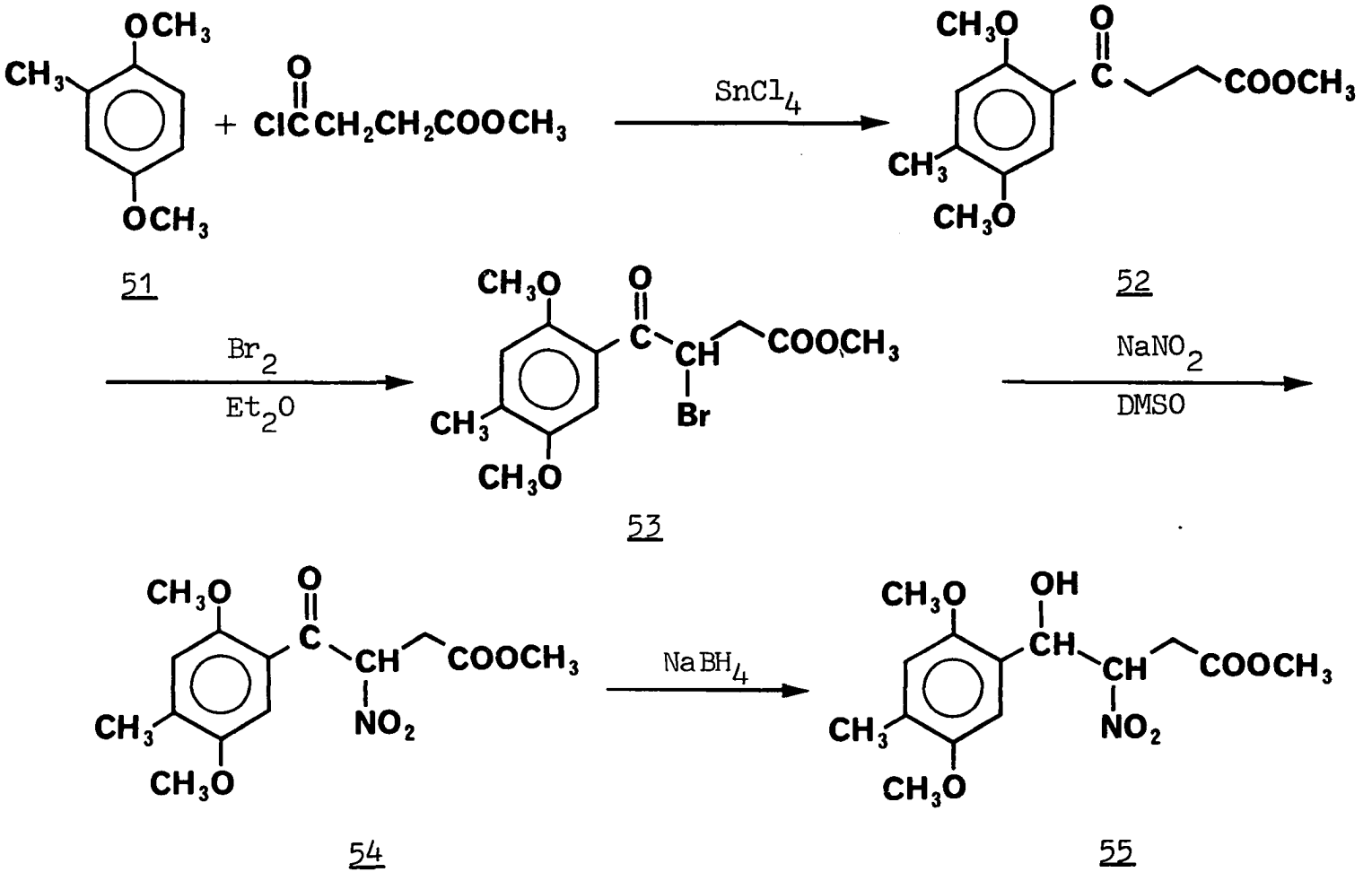
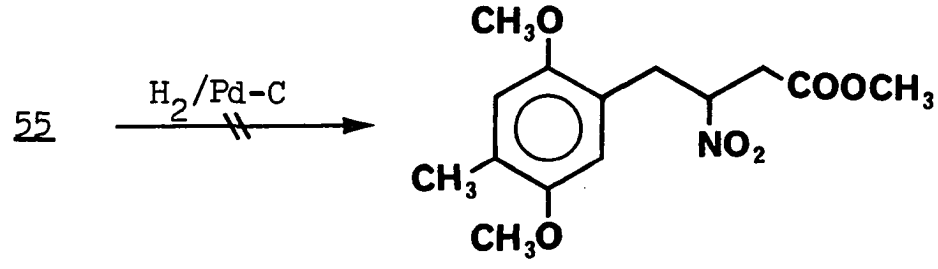
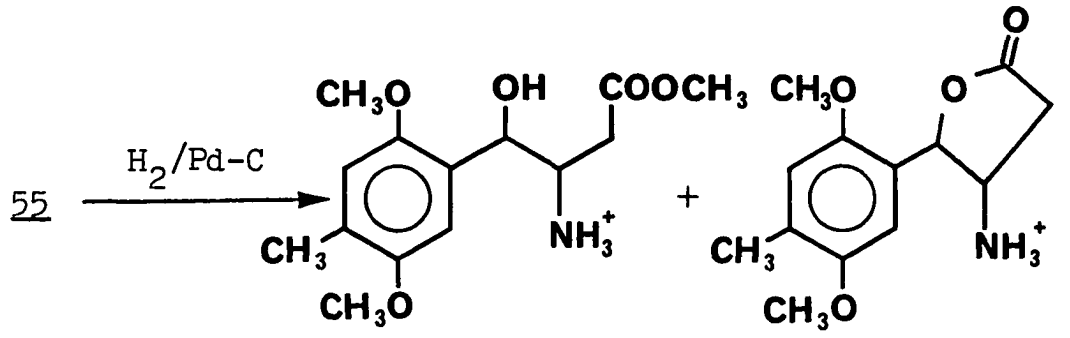


FIGURE 5. (Continued)



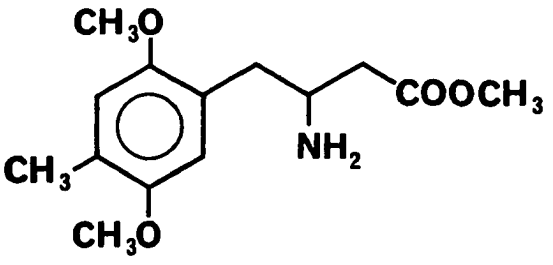

56

for $NH_3^+$, at 3350 $cm^{-1}$ for the hydroxyl of 57, and two carbonyl bands at 1740 $cm^{-1}$ and 1775 $cm^{-1}$ for 57 and 58, respectively. The only other material isolated from the




57 58

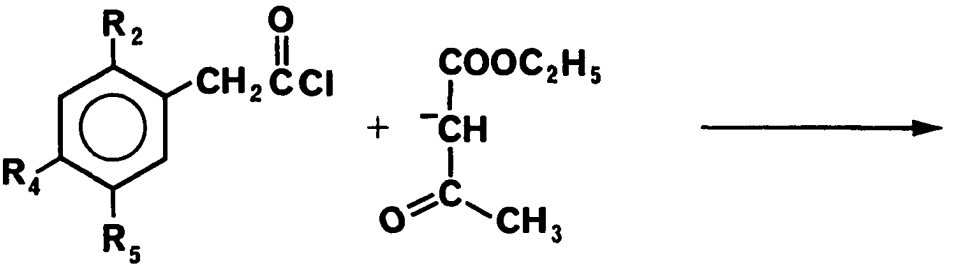
reduction was identified as unreacted 55. Since nitroester 56 was desired, this approach was abandoned without further attempts to selectively remove the benzylic oxygen. It seems likely that 57 or 58 could be further reduced to the amino ester 59, which could be a useful intermediate. However, this route was not pursued further.




59

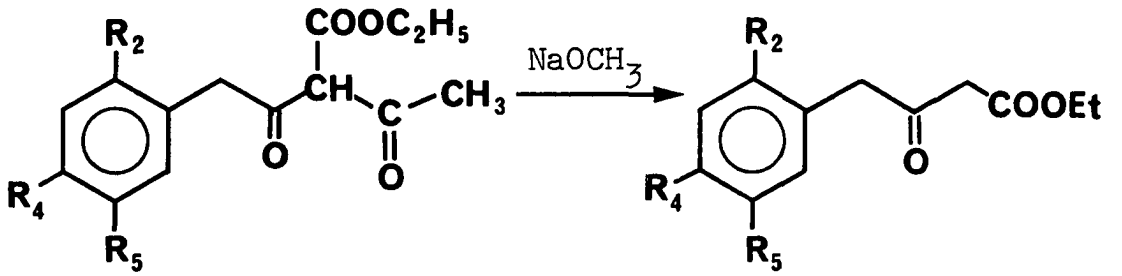
A second approach was based on a modification of the method of Libermann, et al,(191) for preparing 4-phenylacetoacetic ester 62a (Figure 6). It was anticipated that

FIGURE 6. PREPARATION OF 4-PHENYLACETOACETIC ESTER



60a $R_2 = R_4 = R_5 = H$

60b $R_2 = R_5 = OCH_3$; $R_4 = CH_3$



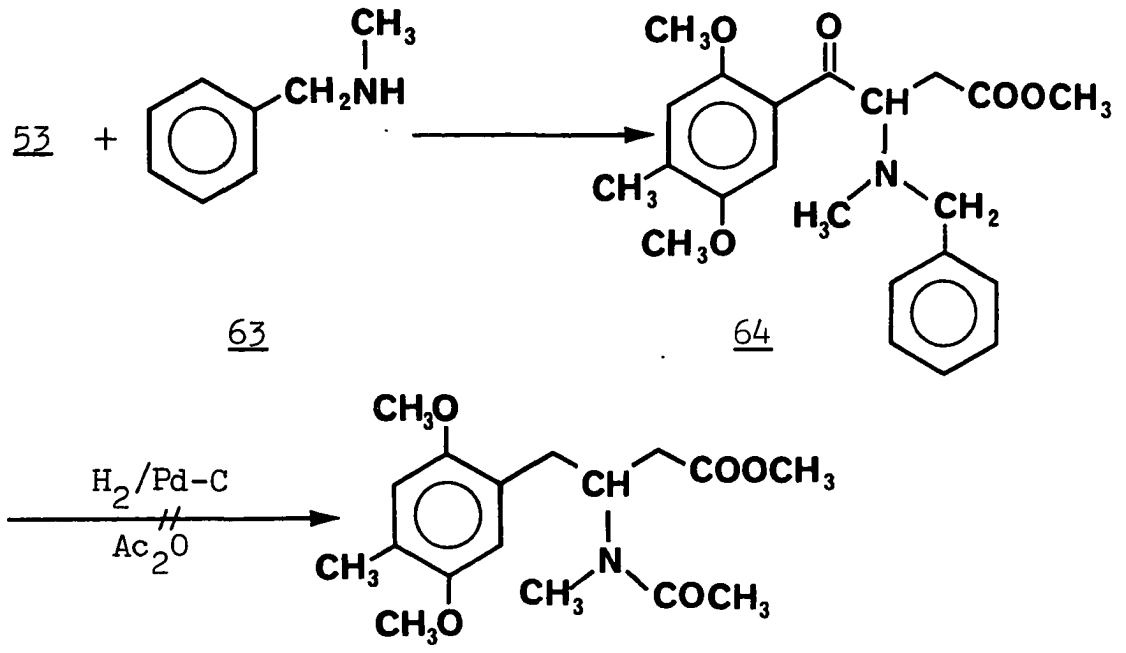
61a; 61b

62a; 62b

the substituted analog 62b could be reductively aminated at the aliphatic keto function to give derivatives of 59. The carboxylic acid precursor for 60b was a known compound and was readily obtained through the sequence $-CH_2Cl \rightarrow CH_2CN \rightarrow -CH_2COOH$ according to the method of Lestina and Cressman (192). The chloromethyl compound was readily prepared by chloromethylation of 2,5-dimethoxytoluene (192,193).

Isolation of the intermediate 61a is reported to be accomplished by stirring the crude condensation products of reaction with cupric acetate, thereupon precipitating the insoluble copper complex. Decomposition of the complex yields 62a. Using this procedure no 61b could be isolated as the copper complex and it was assumed that reaction had not taken place. No further effort was directed toward the preparation of 62b.

A third approach briefly considered is the condensation of 53 (Figure 5) with N-methylbenzylamine 63 to give the aminoketone 64, followed by hydrogenolysis in acetic anhydride to give 65, the N-methyl-N-acetyl derivative of 59.



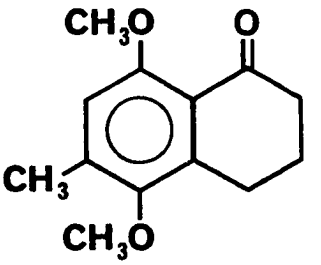

63 64

65

This condensation proceeded smoothly and a 70% yield of 64 was obtained. Debenzylation of 64 took place readily over 10% Pd-C in acetic anhydride. Addition of perchloric acid and further shaking caused rapid and excessive hydrogen uptake which led to a mixture of unidentified products. This route was also abandoned.

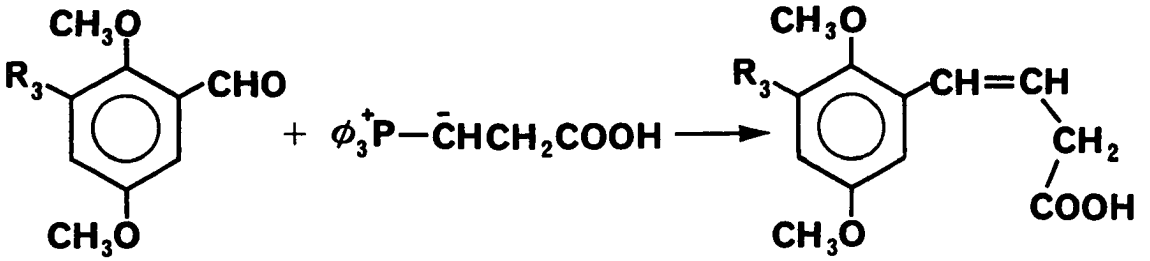
It should be emphasized that each of the three approaches considered to this point bears potential utility in the synthesis of 44 or its N-methylated derivatives. Investigation of each of these schemes was carried out only on a cursory level since they all appeared to be novel approaches and might have potential in a facile synthesis of 44. However, since straightforward literature procedures already existed, further development of any of the three routes did not seem justified.

Attempts to functionalize the side chain before cyclization were abandoned and it was decided to devote attention to the preparation of 66 as a key intermediate in the synthesis of 44. Two approaches were considered. The first




66

was reaction of aldehyde 67 with carboxyethyltriphenylphosphonium ylid to give the butenoic acid 68 (194). This could

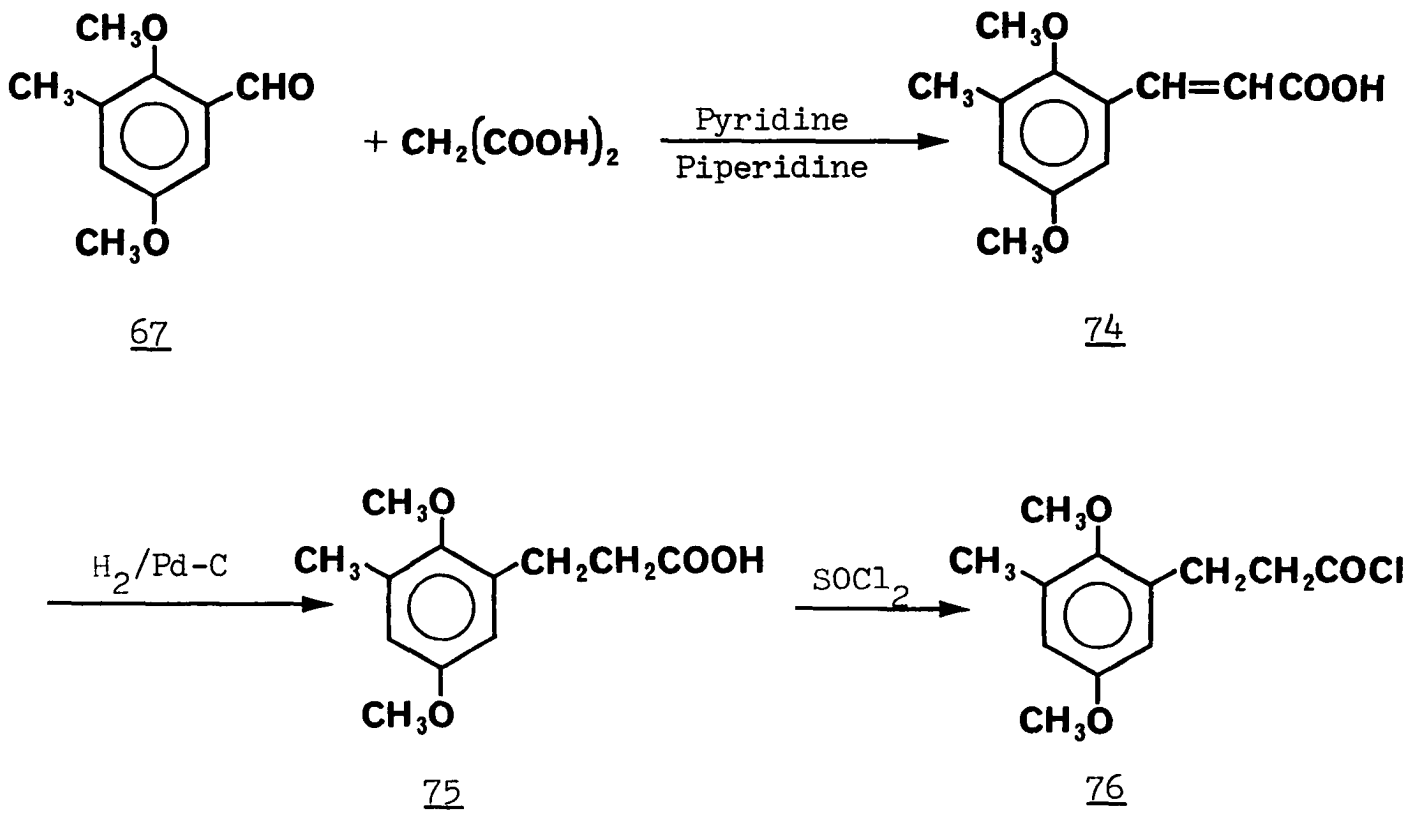



67 $R_3 = CH_3$ 68

69 $R_3 = H$ 70

be reduced to the saturated acid and then cyclized directly to 66. Collaborative attempts with another worker in this laboratory to prepare the homologous 70 by this method gave yields of only about 5%, and it was decided that the method would probably be unsatisfactory without substantial development effort. The method of Elmore and King (195) appeared most practical for the preparation of 66. A slight modification of this procedure is outlined in Figure 7. A variation of the side chain extension used by Krunnfusz (196), which eliminates the need for diazomethane, was also considered, but the method was felt to have no particular advantage over Elmore and King's procedure. Steps leading to 66 by this scheme are high-yielding and give clean products. Aldehyde 67, the starting material, has been reported in the literature (197) and was prepared as shown in Figure 8.

FIGURE 7. ROUTE FOR THE SYNTHESIS OF 3,4-DIHYDRO-5,8-DIMETHOXY-6-METHYL-1(2H)-NAPHTHALENONE 66




67 74

75 76

FIGURE 7. (Continued)

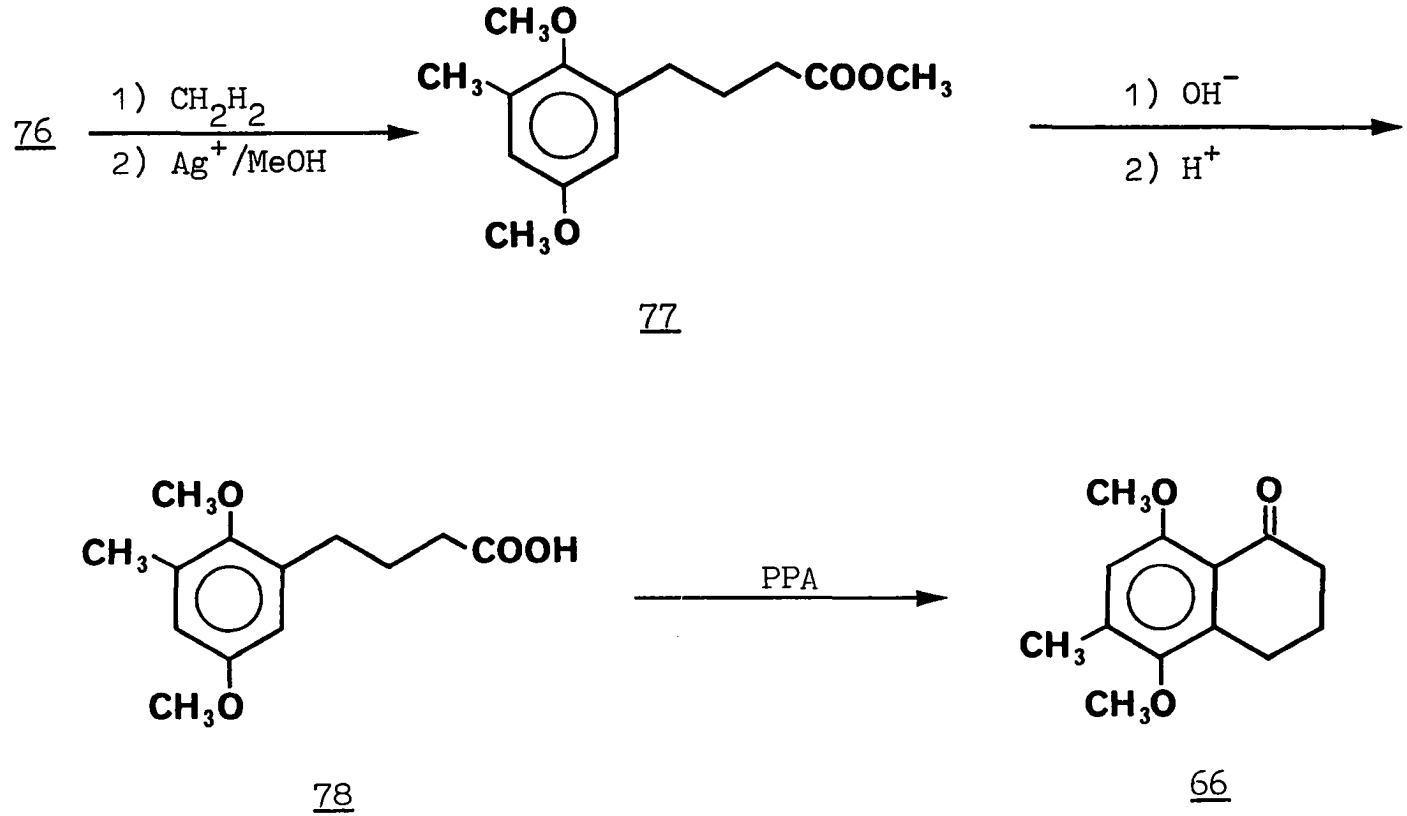
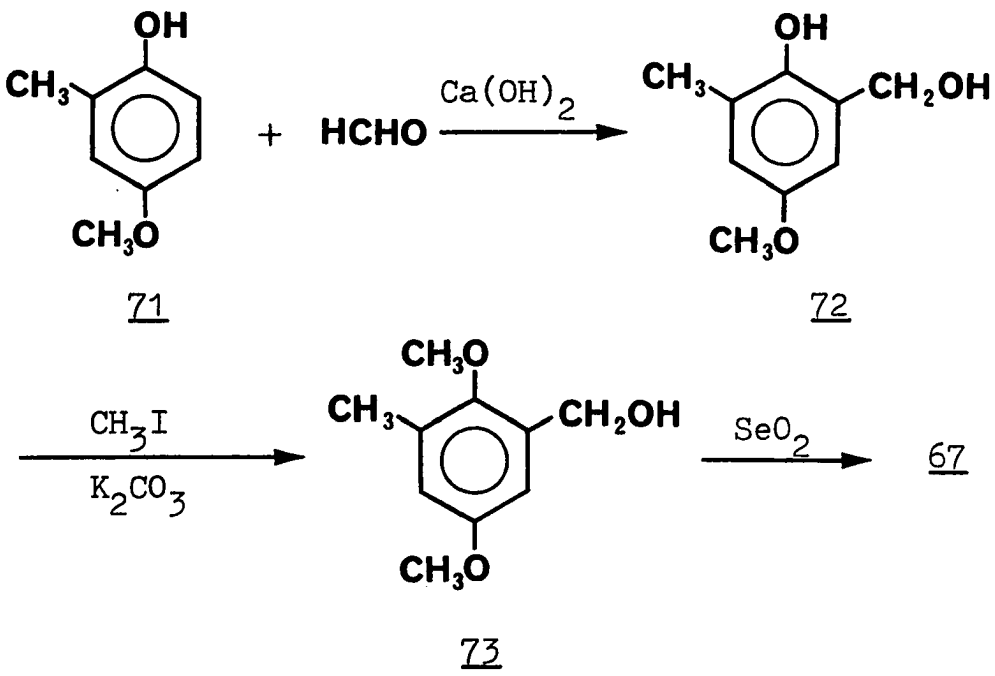
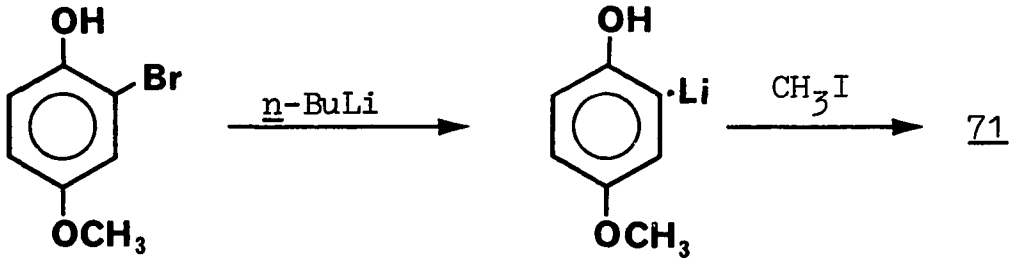


FIGURE 8. SCHEME FOR THE PREPARATION OF 2,5-DIMETHOXY-3-METHYLBENZALDEHYDE

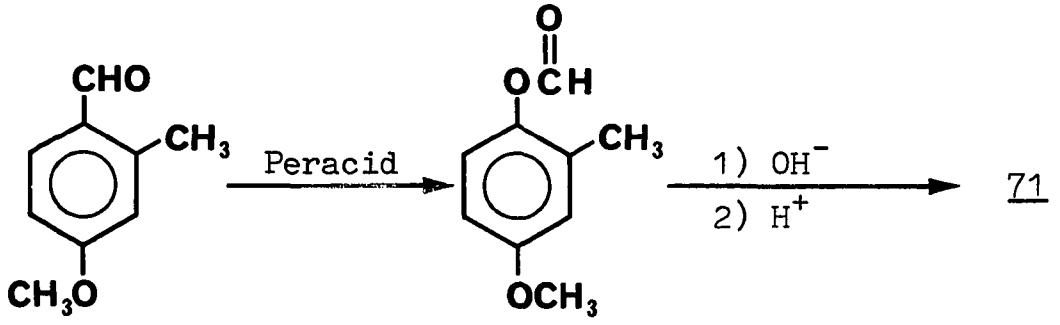



The difficulty in obtaining the phenol 71 proved to be the major obstacle in this scheme. The material is not commercially available and literature syntheses are inconvenient. Para-methoxy-O-cresol has been reported synthesized in low yield by selective monomethylation of methylhydroquinone (190). Attempts to improve this method by using various alkylating agents and modifying conditions were unsucessful in raising the yield beyond the range 10-15%. Since substantial quantities of 71 were desired this approach seemed unsatisfactory. The following sequence has also been reported for the preparation of 71 (199):




This method too appeared unsatisfactory for the large-scale preparation of 71.

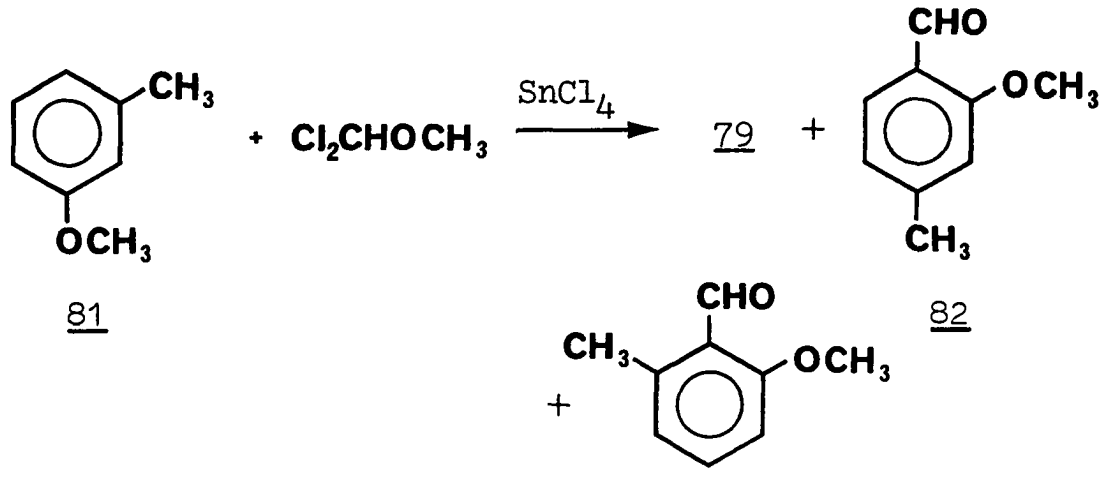
Another approach considered was the conversion of 79 to 71 via the formate ester 80. This transformation could




79 80

be accomplished by a Baeyer-Villiger reaction, followed by base hydrolysis of the resulting ester. Attempts to prepare 79 by formylation of 81 by the method of Rieche, et al,(200) led to mixtures of 79, 82, and 83 in the approximate ratios of 5.5:4.5:2 as determined by integration of the nmr absorptions of the aromatic methyl and aldehydic protons.

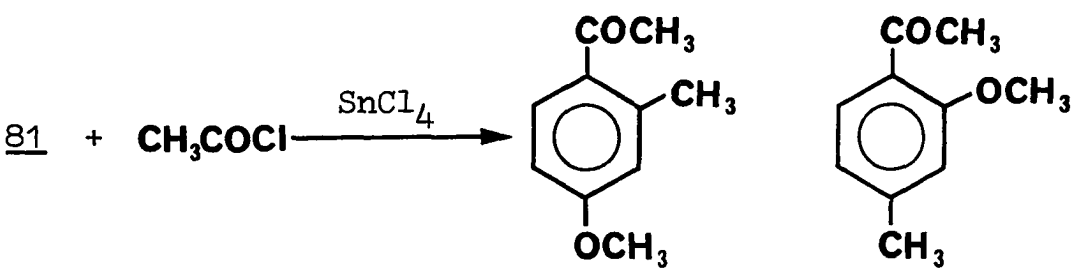
Although 83 could be removed from the mixture by distillation, a mixture of 79 and 82 was not separable and had a 1-2° boiling range. Comparison of the ir spectrum of the




product mixture of 79 + 82 with the published spectrum (201) of 79 showed that the two spectra were superimposable. Attempts to obtain commercial material (Aldrich) for comparison were unsuccessful; the item apparently has been discontinued. Gatterman (202) first reported the synthesis of 79 in 1898 by reaction between 81, HCN, and $AlCl_3$. Royer, et al,(203) reported the systhesis of 79 by a Vilsmeier reaction on 81. Royer's group subsequently reduced their product by a Wolff-Kishner reduction to give 3,4-dimethylanisole. The methyl ether was cleaved to give 3,4-dimethylphenol which had physical properties identical to authentic

material prepared by another route. The non-selectivity of Rieche's method seems somewhat surprising in view of reported preparations by these other workers. It is difficult to explain why the dichloromethyl methyl ether-stannic chloride formylation should be less selective than Gatterman's method.

Acetylation of 81 with acetyl chloride-stannic chloride

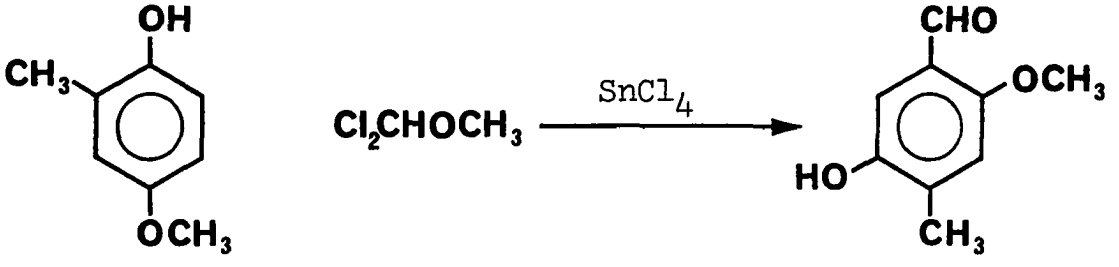



84 85

also led to a mixture of products presumed to be 84 and 85, in the approximate ratios of 2:1 based on integration of the aromatic methyl proton absorptions in the nmr. This mixture could not be separated by fractional distillation and only slight separation was obtained on tlc (silica gel-ether). Even less separation could be obtained for mixtures of 79 and 82 in the same system.

Although the desired phenol 71 could be isolated from mixtures resulting from the direct base hydrolysis of the aldehyde mixture 79 + 82, continuation of this route with crude mixtures was deemed an undesirable alternative.

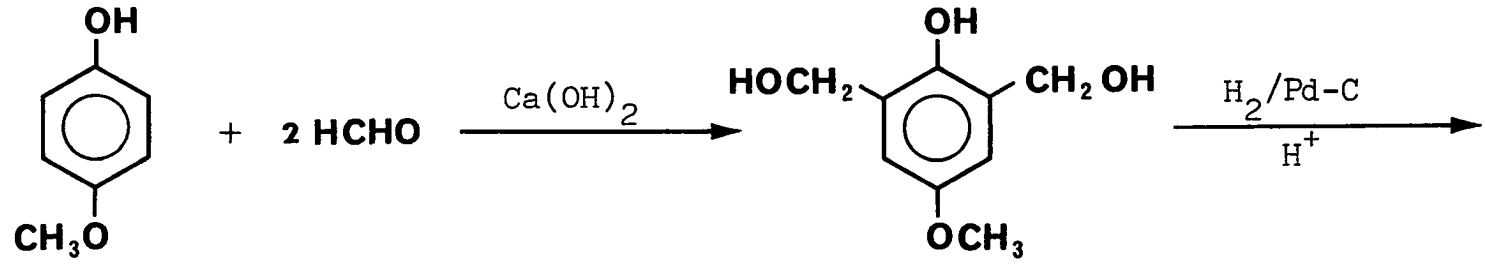
A small amount of the phenol 71 which was obtained was formylated by the method of Rieche, et al (200). The only product obtained was 2-methoxy-4-methyl-5-hydroxybenzaldehyde 86. This is contrasted with the base-catalyzed Lederer-Manasse condensation which gives substitution ortho- to the phenolic function.



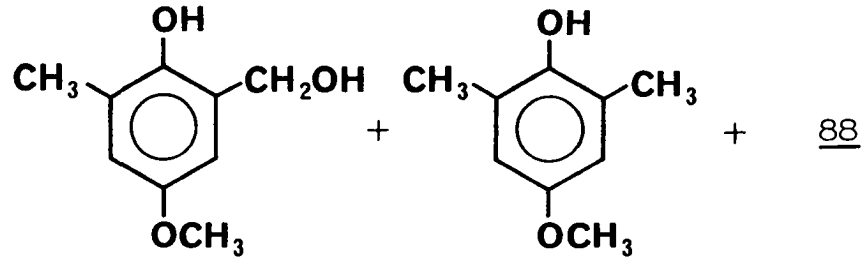

71 86

The approach to the preparation of aldehyde 67 which finally proved successful bypassed the need for phenol 71. The Benzylic alcohol 73 (Figure 8) was prepared directly by the route outlined in Figure 9. The dihydroxy phenol 88 was prepared by a modification of the method of Moran, et al,(204). Base-catalyzed Lederer-Manasse condensation of 87 with two moles of formaldehyde gave the di-hydroxymethyl compound 88 in 62.7% yield, which was isolated as a

FIGURE 9. IMPROVED METHOD FOR THE PREPARATION OF 2,5-DIMETHOXY-3-METHYLBENZYL ALCOHOL

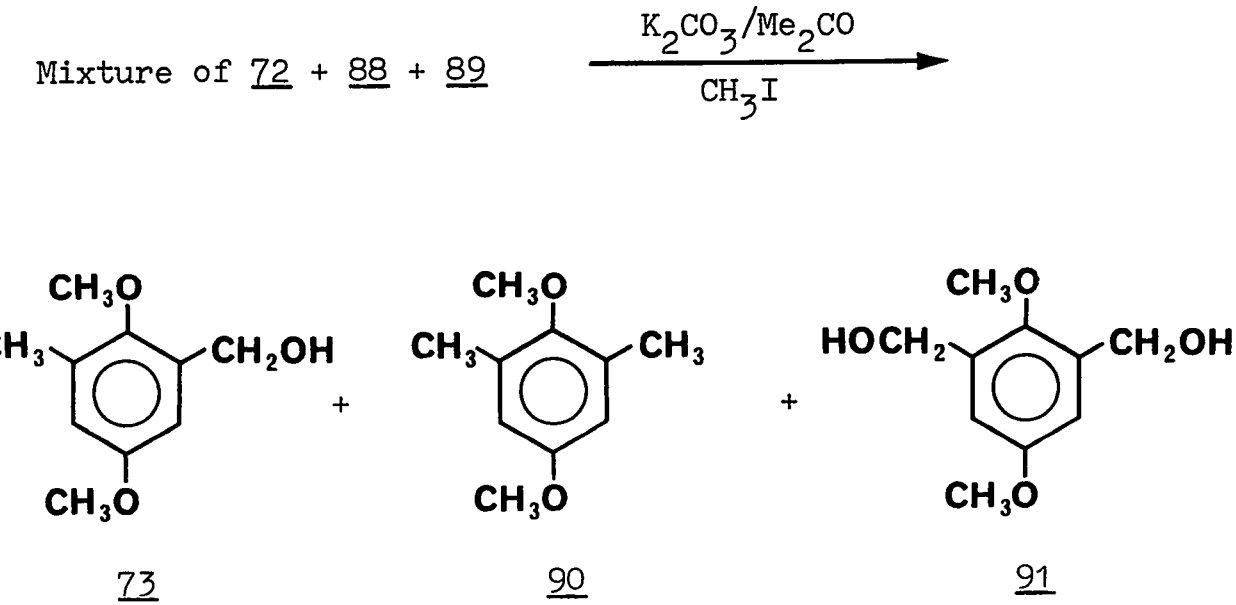



87 88




72 89

FIGURE 9. (Continued)




73 90 91

crystalline, somewhat air-sensitive solid after recrystallization from water. Hydrogenolysis of 88 was carried out in 95% ethanol containing a small amount of sulfuric acid catalyst. Hydrogen uptake was rapid at 50° using 10% Pd-C catalyst, and reduction was stopped after one mole of hydrogen had been absorbed. The catalyst was removed and the ethanol was evaporated. Separation of 72 from 88 or 89 could not be effected by crystallization. It has been established previously (197) that 72 cannot be purified by distillation without decomposition, so the crude reduction mixture was directly O-methylated with methyl iodide and potassium carbonate in dry acetone. The desired benzyl alcohol 73 could be readily separated from other O-methylated products by vacuum distillation and was obtained in an overall yield of 45.5%, based on 88. This yield was considered quite acceptable since 88 could be prepared in large quantities from inexpensive materials.

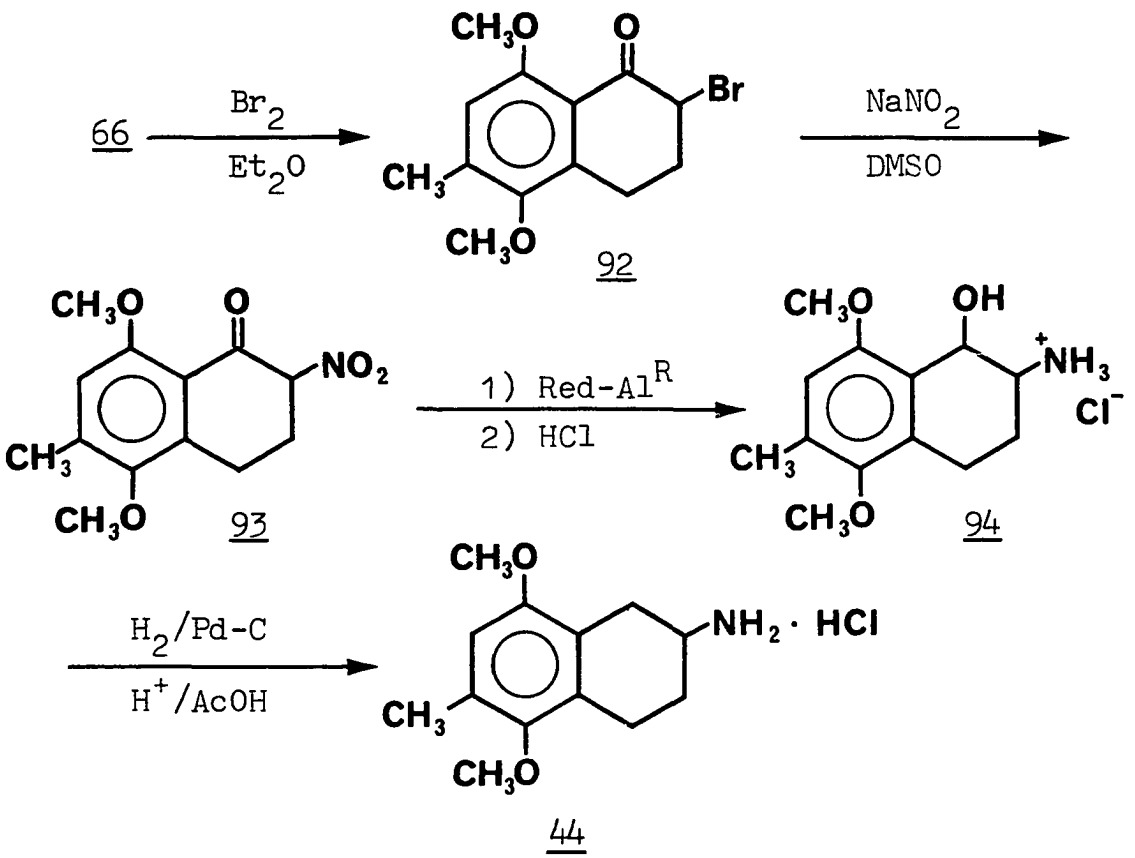
The desired aldehyde, 67, was obtained by oxidation of alcohol 73 using activated manganese dioxide (205) in benzene. The $MnO_2$ was then removed and the benzene evaporated. Pure aldehyde was obtained in 83.5% yield after recrystallization from hexane. The material was identical by ir and nmr analysis to a sample of the aldehyde prepared by the method of Sayigh, et al (197). Oxidation with manganese

dioxide represents an improvement over oxidation with selenium dioxide, both in ease of operation and purity of product.

Condensation of aldehyde 67 with malonic acid in pyridine containing piperidine catalyst (206) occurred readily, and 74 was obtained in 97% yield after recrystallization (Figure 7). Cinnamic acid 74 was quantitatively reduced to 75 which was then converted to the acid chloride 76 by refluxing with thionyl chloride in diethyl ether. An attempt to prepare 76 without the ether as solvent led to extensive decomposition. The acid chloride was then treated with diazomethane, followed by silver benzoate-catalyzed Arndt-Eistert rearrangement in methanol (195,207). The methyl ester 77 was obtained as a viscous straw-colored oil after vacuum distillation in a yield of 88%. Analytically pure 77 was obtained by recrystallization from hexane-ether. Basic hydrolysis of 77 gave a quantitative yield of the acid 78 which was then cyclized in polyphosphoric acid (208) to give the desired α-tetralone 66. The tetralone was isolated as a crystalline hydrate of undetermined composition after recrystallization from ether-hexane. The ir spectrum showed a sharp O-H stretching vibration at 3560 $cm^{-1}$, and the nmr ($CDCl_3$) showed a $D_2O$-exchangeable singlet at δ2.02, integrating for 3 protons (1.5 $H_2O$). In vacuum, the hydrate rapidly decomposed with loss of water to give unhydrated 66

which was characterized as a viscous oil after vacuum distillation. The stoichiometry of the tetralone hydrate was not precisely determined. Values obtained by elemental oxygen analysis, thermogravimetric analysis, or integration of the HOH absorption in the nmr gave variable results indicating values of about 1-1.5 water molecules per molecule of tetralone. It is possible that the product, as initially isolated, is primarily the tetralone·1.5 $H_2O$, which then loses varying amounts of water during handling.

The conversion of the tetralone to the aminotetralin 44 was accomplished by the following scheme:



This route represents a method developed by several workers in this laboratory for the preparation of 2-amino-tetralins (86,87). Sprenger (209) and Kim (210) have used the Neber rearrangement to introduce an adjacent amino function into α-tetralones. It has been observed previously by workers in this laboratory that tosylates of α-tetralone oximes could not be prepared when the parent tetralone possessed a methoxyl in the "8" position. Since oxime tosylates are the intermediates in the Neber rearrangement, utilization of this method was precluded. There may be at least two explanations for the failure to obtain the oxime tosylate. First, the O-H of the oxime may be stabilized by hydrogen-bonding to the aromatic methoxyl oxygen (however, the seven-membered ring which would result is not particularly favorable), or, second, the 8-methoxyl could provide enough steric bulk to prevent the approach of the large sulfonyl chloride moiety.

Although other methods are available for introduction of the amino group adjacent to the ketone (84,211), the route outlined has been found to be convenient and the intermediates are easy to characterize.

Bromination of 66 in diethyl ether with elemental bromine took place readily to give 92 in good yield. Stirring 92 with sodium nitrite and phloroglucinol in DMSO at

room temperature gave, after work-up and crystallization from ethanol, a 63.7% yield of the nitro compound 93. The nitrite displacement of bromine is based on the method of Kornblum (212), for the preparation of α-nitroesters from the corresponding α-haloesters. The nitrotetralone 93 was then reduced in benzene with bis-(2-methoxyethoxy)-aluminum hydride (Red-Al$^{R}$; Aldrich Chemical Co.). The reduction could be accomplished with LAH in diethyl ether or THF, however, the nitrotetralones were found to have low solubility in these solvents. It is more convenient to use benzene as the solvent, in which both the nitro compound and the reducing agent are soluble. Aminoalcohol 94 was isolated as its hydrochloride salt, which was extremely hygroscopic, and was used without further purification. The intermediate erythro and threo aminotetralols of similar systems have been isolated and characterized by other workers in this laboratory (213). Hydrogenolysis of 94 was accomplished by a modification of the method of Sprenger and Cannon (214). Reduction took place readily at room temperature over 10% Pd-C in acetic acid containing a trace of perchloric acid. Higher temperatures were not used due to a propensity for reduction of the aromatic ring under mild conditions, previously observed in this laboratory. Reduction of methoxylated aromatic rings at low pressure has been documented (215).

The desired aminotetralin 44 was isolated from the reduction mixture and obtained as the hydrochloride in 43.5% yield. Treatment with charcoal and recrystallization from isopropanol gave analytically pure material.

Examination of the nmr spectrum of 44 revealed that an unexpected parameter had been introduced. Whereas both DOM 4 and 5,8-dimethoxy-2-aminotetralin (ADT) 28 have a single absorption for the methoxyls at δ3.78 (free amine in $CDCl_3$), compound 44 showed two distinct singlets at δ3.72 and δ3.80. Molecular models show that in 44 the interaction of the 5-methoxyl with the 6-methyl and the C-4 methylene protons causes sufficient steric interference to force the 5-methoxyl protons to lie somewhat out of the plane of the aromatic ring. This would cause removal of these protons from the deshielding zone around the ring and would result in a shift of the 5-methoxyl protons upfield of that observed for the in-plane 8-methoxyl. The nmr spectrum of 5,8-dimethoxy-1-tetralone shows methoxyl absorptions at δ3.75 and δ3.78, or δ0.03 apart. In the 6-methyl homolog 66 however, the methoxyls appeared at δ3.72 and δ3.90, separated by δ0.18. The additional shift of 0.15δ over that observed for 5,8-dimethoxytetralone was also felt to be primarily attributable to the out-of-plane methoxyl. Thus,

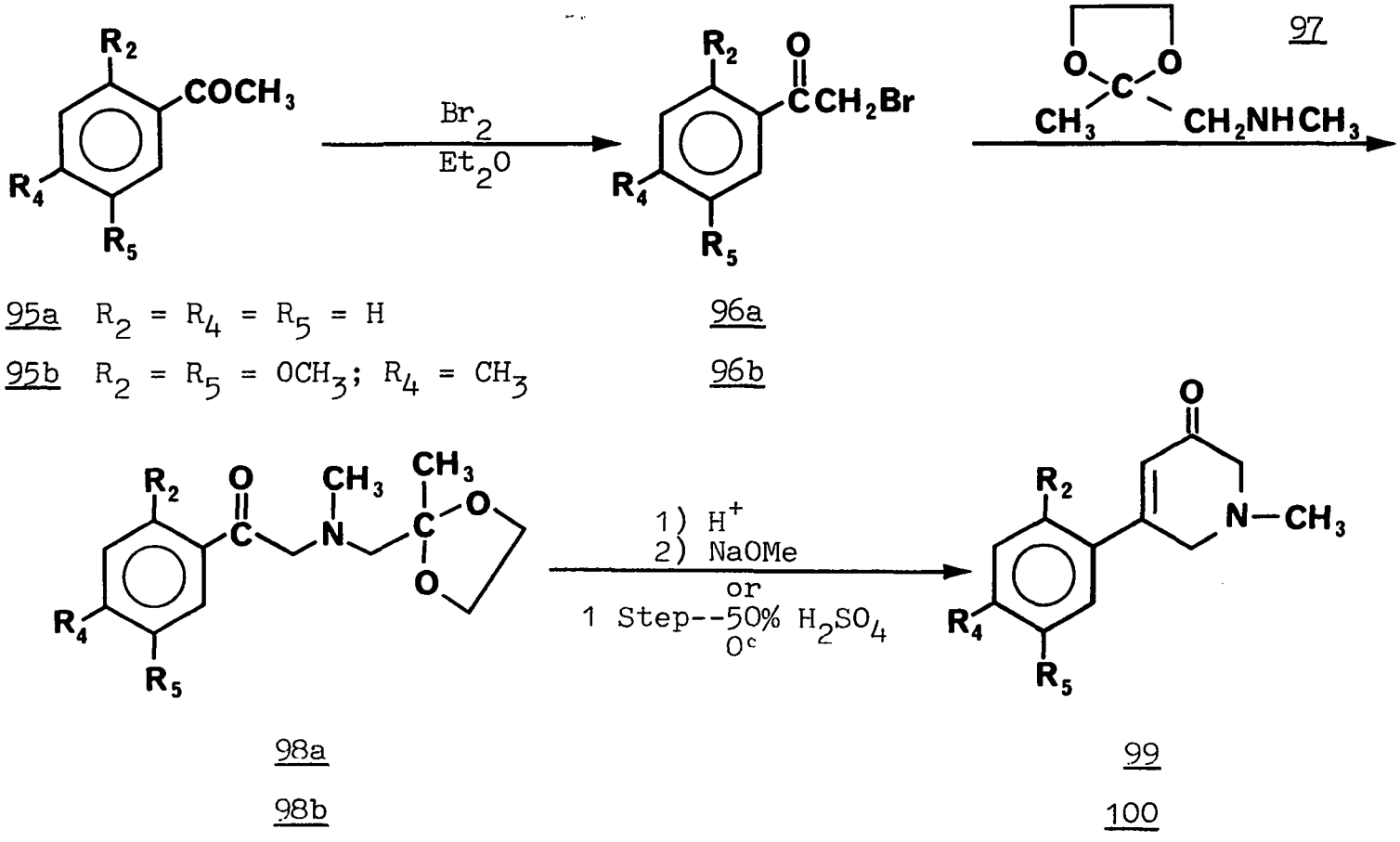
44 may not be a good model for a rigid DOM conformation, since the nmr of DOM indicates that both methoxyls lie in the plane of the ring, whereas in 44 they do not.

## Part III. A Discussion of Attempts to Prepare An LSD AD-Ring Congener, And to Synthesize N-Methyl-5-Carbethoxy-3-Piperidone As An Intermediate

Three potential routes were considered for preparation of the LSD A-D system 45. The first of these is outlined in Figure 10 and is based on Kornfeld, et al's (216), original procedure for the synthesis of lysergic acid. It was envisioned that the α,β-unsaturated ketone 99 or 100 could be functionalized at the ketonic function in a number of ways.

Acetophenone 95b was prepared in 89% yield by acetylation of 2,5-dimethoxytoluene. Bromination of 95b by Wild's procedure (217) gave the bromoketone 96b in 82% yield. Bromo compounds 96a or 96b were readily condensed with methylaminoacetone ethylene ketal 97 to give 98a or 98b in good yield. Attempts to prepare the model system 99 by acid-catalyzed ketal cleavage, followed by sodium methoxide cyclization similar to the method of Kornfeld, et al (216) and to the method of Cymerman Craig, et al (218), or by direct one-step treatment with 50% sulfuric acid at 0° following the method of Leeman and Fabbri (115) led to complex

FIGURE 10. A MODIFICATION OF KORNFELD AND CO-WORKERS (216) METHOD FOR THE PREPARATION OF LSD AD-RING PRECURSORS



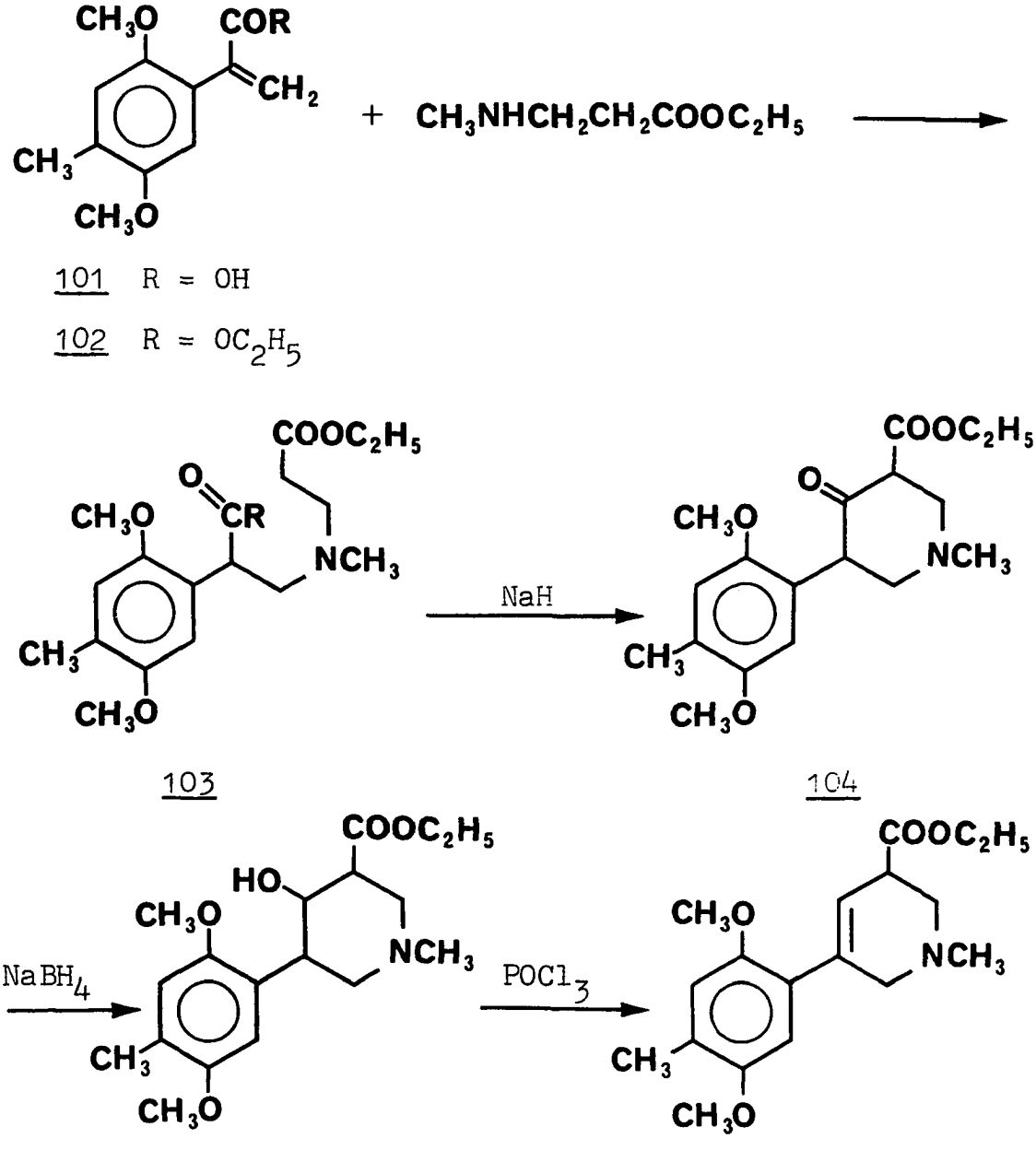

95a $R_2 = R_4 = R_5 = H$ 96a

95b $R_2 = R_5 = OCH_3$; $R_4 = CH_3$ 96b

98a 99

98b 100

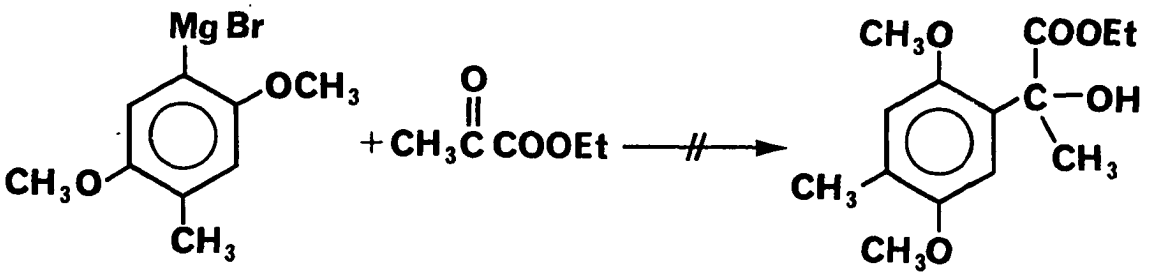
FIGURE 11. PROPOSED PREPARATION OF AN LSD AD-RING CONGENER BY A MODIFICATION OF THE METHOD OF HOHENLOHE-OCHRINGEN (49)



mixtures from which no identifiable material could be isolated. This result discouraged further development of this route and actual work with 98b was not begun. Kornfeld (216) has noted, and this has been confirmed by Cymerman Craig (218), that systems similar to 99 are extremely sensitive to air oxidation. It was felt that even if attempts to prepare 100 were successful, the material might be so labile to oxidation that problems might arise in subsequent handling.

A second route which was briefly considered was a combination of the methods of Hohenlohe-Ochringen (49) and Horii, et al (90). The application of this method is outlined in Figure 11. The 2,5-dimethoxy-4-methylphenylacrylic acid 101 has been reported prepared by a multistep sequence (219). However, Lapkin and Golovkova (220) have reported the synthesis of esters of substituted phenyl lactic acids by a simple one-step reaction between a phenyl Grignard reagent and ethyl pyruvate. It was anticipated that the 2-phenyl lactic ester 106 could be dehydrated to the corresponding acrylic ester 102 by refluxing in acetic acid (221).

The Grignard reagent 105 was easily obtained by the method of McHale, et al,(222) from 2,5-dimethoxy-4-bromotoluene, which was prepared by a modification of the method of Harley-Mason (163). Reaction between the Grignard

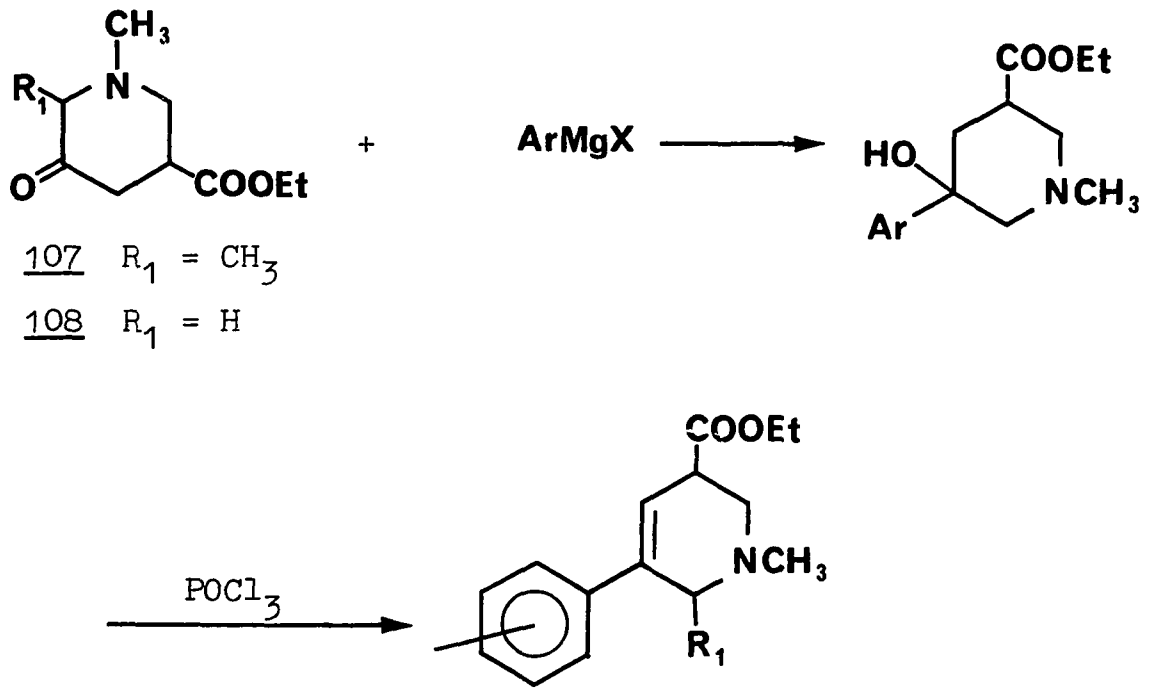



105 106

reagent and ethyl pyruvate, after work-up, failed to yield material which could be identified as 106. Substantial quantities of 2,5-dimethoxytoluene were identified, a finding which indicated that the Grignard reagent had abstracted an active hydrogen, probably from the pyruvate ester. No further effort was directed toward preparation of 102.

Both of the above routes suffer from the disadvantage that the starting materials 95b and 102 must have the ring substitutions desired in the final compound. It was felt that a more general route which would allow for preparation of a number of other ring-methoxylated A-D systems was desirable and the route of Plieninger (37) was examined. This route (Figure 12) involves treatment of 1,2-dimethyl-5-carbethoxy-3-piperidone 107 with an aromatic Grignard reagent, followed by dehydration. It has been noted earlier that the methyl group in Plieninger's compound ($R_1$) may not be necessary and accordingly preparation of the analogous

FIGURE 12. PREPARATION OF AN LSD AD-RING CONGENER BY PLIENINGER'S METHOD (37)




107 $R_1 = CH_3$

108 $R_1 = H$

108 was undertaken. A modification of Plieninger's procedure was used (Figure 13). Formyl succinate 110 was prepared by condensation between diethyl succinate and ethyl formate in the presence of sodium metal by the method of Wislicenus (223). This was condensed with ethyl sarcosinate 111 in refluxing benzene with continuous water removal to give the enamine 112 in good yield. The enamine crystallized on standing. Reduction of 112 with sodium cyanoborohydride following the method of Borch, et al,(224) gave the

FIGURE 13. PROPOSED SYNTHESIS OF N-METHYL-5-CARBETHOXY-3-PIPERIDONE

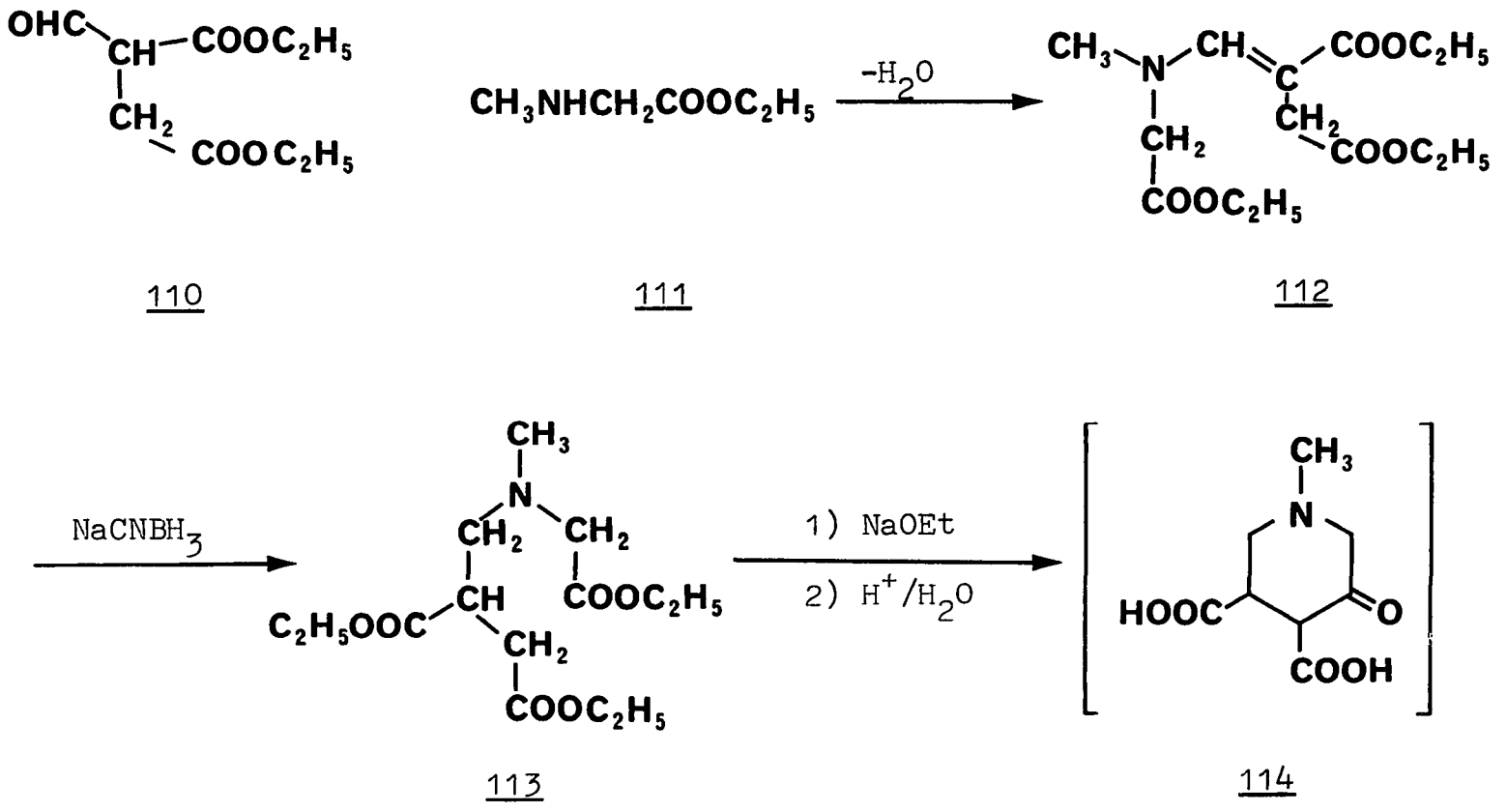
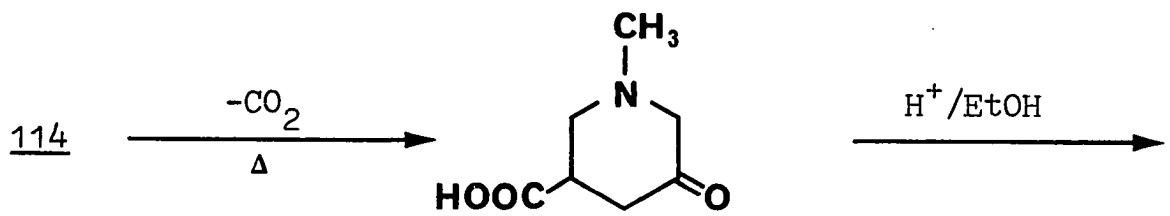
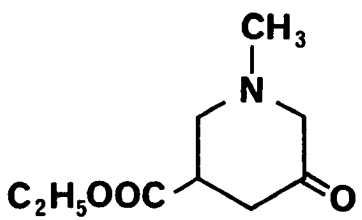


FIGURE 13. (Continued)




115




108

triester 113 in 96% yield. Dieckmann cyclization of 113 utilizing sodium ethoxide in toluene was run in the usual way, the reaction was then quenched with acid and the intermediate ketodiester decarboxylated in refluxing toluene. The reaction mixture was taken to dryness and stirred with dry HCl-ethanol for 96 hr. The product isolated after work-up and distillation could not be identified as the expected ketoester 108. Nmr analysis of the crude mixture showed 2 separate absorptions for N-methyl protons at δ2.33 and δ2.47. The ratios of the magnitudes of these absorptions varied from one preparation to the next but the signal at δ2.47 was always present in proportions from approximately 40% to as much as 90% in some cases. This mixture was shown by tlc analysis (silica gel-ether) to consist of three major components and was subjected to preparative column chromatography over silica gel and eluted with ether. Four components were isolated whose $R_f$ values on tlc (silica gel-ether) and percent composition in the effluent from the column are shown.

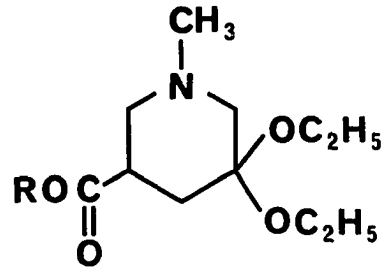
| Component | $R_f$ | Percent Recovery |
|---|---|---|
| "1" | 0.55 | 60.5 |
| "2" | 0.47 | tr |
| "3" | 0.35 | 7.0 |
| "4" | 0.20 | 32.5 |

Component "2" could not be isolated in sufficient quantities for identification. Components "1," "3" and "4" were investigated to determine which was the expected ketoester 108.

Components "1" and "3" had carbonyl absorptions in the infrared at 1730-1740 $cm^{-1}$, component "4" however had two carbonyl absorptions; one at 1760 $cm^{-1}$ and one at 1732 $cm^{-1}$. The abosrption at 1760 $cm^{-1}$ was considered unusual since esters and six-membered cyclic ketones would be expected to absorb in the range 1725-1740 $cm^{-1}$. The possibility that the compound contained a six-membered lactone ring, which might be expected to absorb at ca 1755 $cm^{-1}$, was eliminated by demonstrating that borohydride reduction selectively destroyed the carbonyl abosrption at 1760 $cm^{-1}$.

The nmr spectra of "1," "3" and "4," while not particularly revealing in the δ1.0-δ2.2 region, nevertheless provided useful information. Absorptions for the N-methyl protons of components "1," "3" and "4" were recorded at δ2.33, δ2.36, and δ2.47, respectively. All three components had ethyl ester absorptions centered at δ4.15-4.20 (q, -O-$CH_2$-$CH_3$). However, component "1" also had two closely-spaced quartets centered at δ3.50 and δ3.57. It was felt that these signals were too far upfield to represent ester linkages but probably were more consistent with values for methylenes adjacent to an ether oxygen. The splitting

pattern indicated that these signals resulted from two ethyl ethers and that they were in approximately the same chemical environment. It was thus postulated that component "1" was the desired ketoester which had been derivatized as the diethyl ketal 116 under the work-up conditions of ethanol and dry HCl.




116 R = Et

117 R = n-hexyl

Molecular models demonstrated the non-equivalence of the two geminal ethoxyls and suggested that this molecule is probably fairly rigid due to unfavorable 1-3 interactions between the carbethoxy, when it is axial, and an axial ethoxyl. Elemental C, H, and N analysis gave values which were in agreement with those calculated for 116. Low resolution 70 eV mass spectral analysis showed no molecular ion at m/e = 259, but low intensity peaks were observed at m/e = 230 and 214. Djerassi (225) has noted that acetals do not usually show a molecular ion but readily lose an alkyl or

alkoxyl to give a peak at M - OR and M - R. Thus the peak at m/e = 214 was rationalized as the M - $OCH_2CH_3$, and the m/e = 230 as the M - $CH_2CH_3$ peak.

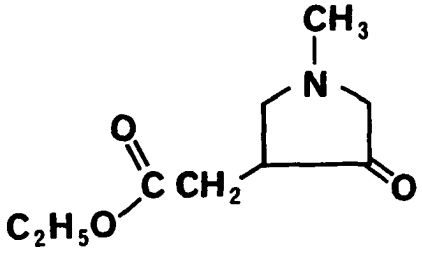
Although it was considered unusual that the ketal had been formed (226) it was expected that selective acid hydrolysis would readily yield the desired keto ester 108. Surprisingly, this was not the case. In 3N HCl the reaction proceeded at reasonable rates only at temperatures of 40-50° C. Using tlc to monitor the progress of the reaction, complete disappearance of starting material 116 occurred after about 4 hr at 50° C. Stirring with 3N HCl at temperatures from 25-40° had little effect, even over periods of 48-72 hr. At 50° it was also found that hydrolysis was extremely slow at pH's above 2. The apparent stability of the ketal was quite startling but more surprising was the finding that, after tlc indicated reaction completeness, only small amounts of material could be isolated. Ir and nmr analysis proved that the hydrolysis product was identical to component "3," originally isolated from the Dieckmann product mixture. Thus it was assumed that this material was the desired keto ester 108. Low resolution 70 eV mass spectral analysis indicated an apparent molecular ion at m/e = 185 and a more prominent M - 1 peak. Djerassi points out that frequently in piperidine compounds αH abstraction gives a prominent M - 1 peak (225). Although the

fragmentation pattern could be rationalized with the expected keto ester, elemental C, H and N analysis of the HCl salt gave neither the expected values nor did it give consistent results. Since the HCl salt decomposes at 96° it seems possible that the compound is not amenable to combustion-type analysis. Although the hydrolysis product gave a positive 2,4-DNP test, it cannot conclusively be proven that in fact the ketoester 108 was obtained.

The failure to obtain substantial quantities of the ketal-hydrolysis product was at first attributed to possible water solubility of the product. To explore this possibility the ethyl ester diethyl ketal 116 was transesterified with sodium metal in 1-hexanol to give the homologous hexyl ester-diethyl ketal 117 and this material was fully characterized. Attempted acid-catalyzed ketal hydrolysis of this compound again demonstrated the stability of the ketal. After hydrolysis the acidic solution was carefully basified with $K_2CO_3$ and extracted repeatedly with ether. Reduction of the ether extracts yielded a small amount of material which had ir and nmr spectral properties nearly identical to that of the ethyl ester ketal cleavage product, with the exception that the ethyl ester was replaced with the hexyl. This material was contaminated with a nearly equal quantity of 1-hexanol, which showed that ester cleavage was taking place. In view of the low yield of hydrolysis product,

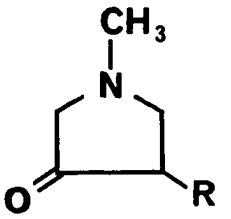
which is relatively pure, and the apparent stability of the ketal, it is suggested that hydrolysis of the ester moiety may take place first, followed by rapid cleavage of the ketal. The ester bulk may induce unfavorable steric interactions in the transition state during ketal hydrolysis. After ester cleavage, removal of these steric restraints may allow facile ketal hydrolysis. Alternatively, anchiomeric assistance from the free carboxyl may also somehow enhance ketal cleavage. This explanation may be more satisfactory, in view of the fact that the ketal was formed in the first place. It is possible that intramolecular hydrogen bonding could stabilize the tetrahedral transition state (226) involved in ketal formation.

The question still remaining is the identity of component "4" from the Dieckmann cyclization. Two pieces of spectral evidence suggested that component "4" was actually the pyrrolidone acetic ester 118. The carbonyl stretching




118

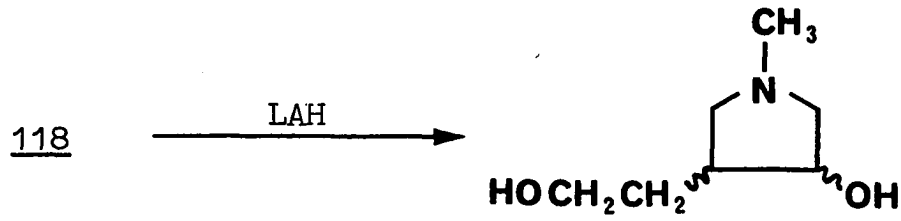
frequency of N-methyl-3-pyrrolidone 119 is reported to be 1765 $cm^{-1}$ (227). Also pyrrolidone ester 120 has a ketone



119 R = H

120 R = COOEt

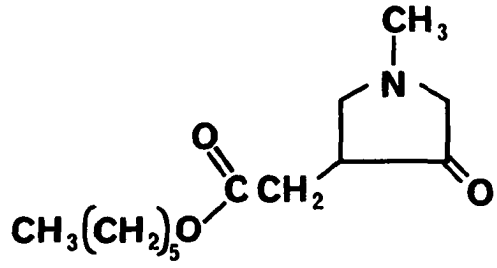
carbonyl absorption at 1759 $cm^{-1}$ (228). Component "4" has a carbonyl absorption at 1759 $cm^{-1}$. The chemical shift of the N-methyl protons in the nmr for component "4" at δ2.47, as compared with δ2.33 for component "1," was also consistent with the observed downfield shift seen for similar 5-membered systems as compared with the six-membered homologs. For instance, the N-methyl protons of N-methylpyrrolidine and N-methylpiperidine are observed at δ2.34 and δ2.10, respectively (229). Low resolution mass spectrometry (70 eV) established a molecular ion at m/e = 185, and results of elemental C, H, N, and O analysis agreed with the predicted values for 118. To verify this structural assignment, 118 was reduced with LAH to the diol 121. The distilled reduction product was composed of nearly equal proportions of the 3,4-cis and trans diols. Although this complicated the nmr spectrum, the methylene protons adjacent




121

to the side chain hydroxyl were split into a broad triplet centered at δ3.70. This splitting pattern could only arise if the original structural assignment was correct.

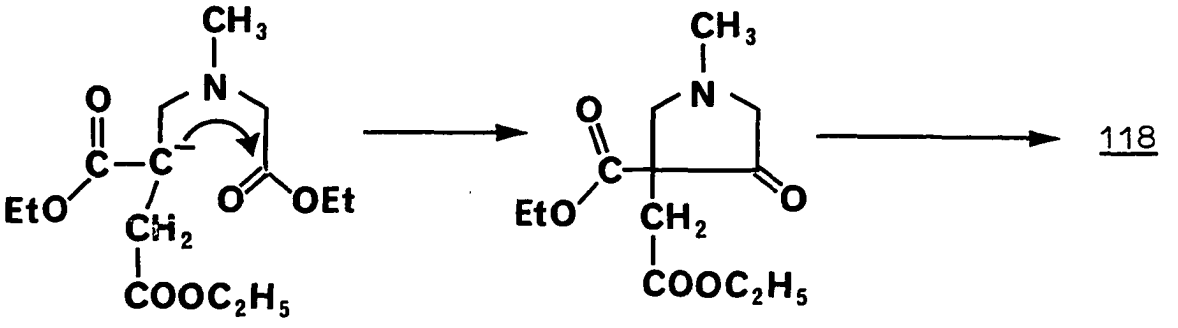
A subsequent Dieckmann cyclization using sodium hydride as the base, after work-up and treatment with 1-hexanol and dry HCl, afforded only the hexyl ester homolog 122 of the




122

five-membered pyrrolidone, with no piperidone isolated. It can be seen from this result that the pyrrolidone derivative is not merely a by-product but may actually be the major isolated product. Formation could occur by two possible routes. Route 1 would appear more likely, although

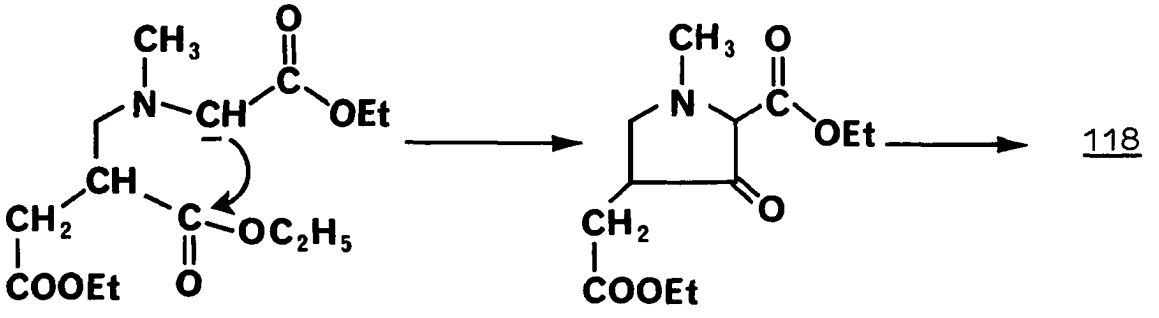
Route 1:




118

-or-

Route 2:

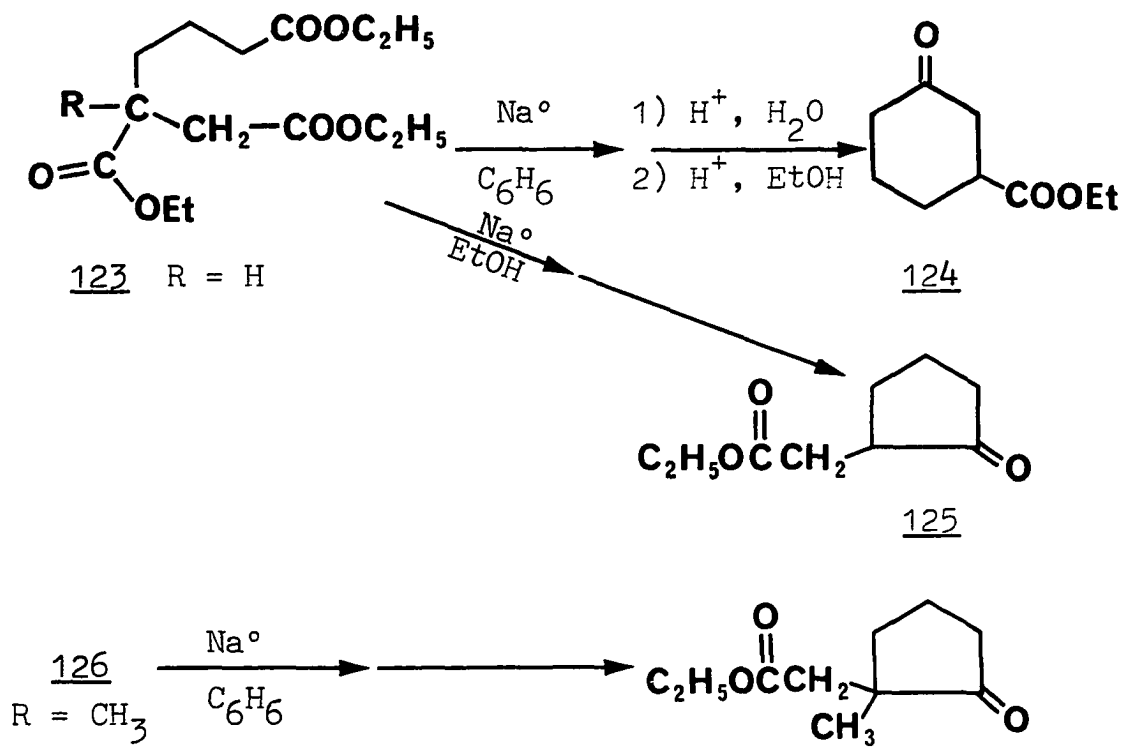



118

precedent has been found for the reactivity of the methylene protons adjacent to the nitrogen (230,231).

The formation of five-membered rings might at first seem unusual. However, some workers have considered it surprising to obtain the six-membered series and they note that in their work the five-membered system is more often produced (232). Although the Dieckmann reaction is widely

used the direction in which ring cyclization takes place still cannot always be predicted (233). For example, triethylpentane-1,2,5-tricarboxylate 123 may be cyclized to the piperidone 124 (232) or to the pyrrolidone 125 (234), depending on the base used to effect cyclization. Introduction of a methyl group into the 2 position as in 126 in exclusive formation of the five-membered ring.




Solvent effects, steric effects, and surface effects of the base used for cyclization have all been offered as explanations for the variable ring sizes obtained when

Dieckmann cyclization can proceed via two alternate pathways (234-237).

In the work discussed here three relevant observations can be made which may be inter-related. First it is entirely possible that Plieninger, in his original work (37), also obtained the five-membered ring or mixtures of it which could not be detected when characterized only by elemental analysis. Second, if Plieninger did in fact obtain the six-membered piperidone, then it seems likely that the different course of Dieckmann cyclization observed in this case is due to the lack of the methyl group, as discussed in the Statement of the Problem, Part III. In any case, it is probably safe to assume that Plieninger did not obtain the diethyl ketal of his material and this can probably be attributed to the steric interference of the methyl group in his compound, whereas in the des-methyl compound this factor is not operating.

# EXPERIMENTAL

All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, and are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, by Midwest Microlab, Ltd., Indianapolis, Indiana, and by the Division of Medicinal Chemistry, University of Iowa. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer using tetramethylsilane as an internal standard. Fluorescence spectra were determined on an Aminco-Bowman spectrophotofluorimeter and recorded on an X-Y recorder. Gas chromatographic analyses were carried out on a Hewlett Packard Model 5750 gas chromatograph equipped with a flame ionization detector. Mass spectra were obtained on a Finnigan Model 1015 Mass Spectrometer. Optical rotations were determined with a Perkin-Elmer Model 141 Polarimeter.

## Part I.

2-Bromo-5-hydroxybenzaldehyde. Prepared by bromination of m-hydroxybenzaldehyde in AcOH by the method of Pandya, et al (178). Yield, 31%. Mp 134-134.5° [lit (179) mp 133°]. ir (KBr) 3200 $cm^{-1}$ (OH); 1690 $cm^{-1}$ (C=O); 1600 $cm^{-1}$ (C=C) (Sadtler, Standard Spectra, Midget edition, infrared spectrogram 42144). nmr (DMSO) δ7.07-7.65 (m, 3, ArH); δ10.18 (s, 1, CHO); (Sadtler nmr spectrum 13422M).

2-Bromo-5-methoxybenzaldehyde 46a. A solution of 20.09 g (0.1 mole) of 2-bromo-5-hydroxybenzaldehyde in 36 ml $H_2O$ contg 8 g (0.2 mole) of NaOH pellets was heated to reflux and 16.38 g (0.13 mole) $(CH_3)_2SO_4$ added. The mixt was stirred vigorously with reflux for 1 hr then was steam distilled until the distillate no longer produced solid material when cooled. The solid was collected by filtrn and dried. Yield, 16.35 g (76%) of 48a mp 73-74.5° [lit (179) mp 75-76°]. ir (mull in mineral oil) 1690 $cm^{-1}$ (C=O) (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42143). nmr ($CDCl_3$) δ3.80 (s, 3, $ArOCH_3$); δ6.8-7.6 (m, 3, ArH); δ10.30 (s, 1, CHO); (Sadtler nmr spectrum 13421M). A small sample was oxidized to the corresponding acid with aqueous permanganate, mp 160-162° [lit (239) mp 161-162°].

3-Bromo-4-methoxybenzaldehyde 46b. Prepared by the method of Gray, et al (177). Yield, 35%. Mp 52-53° [lit (177) mp 53°]. ir (KBr) 1670 $cm^{-1}$ (C=O). nmr ($CCl_4$) δ3.98 (s,3, $ArOCH_3$); δ6.88 and 7.0 (2s, 1, ArH); δ7.6-8.07 (m, 2, ArH); δ9.74 (s, 1, CHO).

3-Hydroxy-4-bromobenzoic acid. Prepared by the method of Hodgson and Beard (179). Yield, 30%. Mp 225-227° [lit (179) mp 226-227.5°]. ir (KBr) 2500-3200 $cm^{-1}$ (COOH); 1700 $cm^{-1}$ (C=O). nmr (DMSO) δ7.24-7.83 (m, 3, ArH); δ11.85 (s, 2, COOH, ArOH).

3-Methoxy-4-bromobenzoic acid. A solution of 39 g (0.18 mole) of 3-hydroxy-4-bromobenzoic acid was prepared in 75 ml $H_2O$ contg 22 g (0.55 mole) NaOH. Dimethyl sulfate 23.2 g (0.20 mole), was added and the soln stirred vigorously and heated to 80° C. A second portion of 9.4 ml of $(CH_3)_2SO_4$ was added and the soln refluxed 2 hr. At this time sufficient 50% NaOH soln was added to clarify the soln and refluxing was continued for 10 min. The soln was cooled, acidified with 6 N HCl and the pptd acid collected by suction filtrn. The acid was recrystallized from MeOH-$H_2O$, mp 219-220° [lit (179) mp 219-220°]. Yield, 33.3 g (80%). ir (KBr) 2500-3200 $cm^{-1}$ (COOH); 1700 $cm^{-1}$ (C=O). nmr (DMSO) δ3.99 (s, 3, $ArOCH_3$); δ7.51-7.69 (m, 3, ArH); (Sadtler nmr spectrum 13425M).

3-Methoxy-4-bromobenzaldehyde 46c. 3-Methoxy-4-bromobenzoic acid 20.8 g (0.09 mole), was refluxed overnight with 52 ml of $SOCl_2$. The $SOCl_2$ was removed *in vacuo* and the residual solid taken to dryness from dry benzene several times. The resulting acid chloride was reduced with $LiAlH(O\text{-}t\text{-}Bu)_3$ according to a modification of the method of Ho, *et al* (180). A soln of 22.9 g (0.09 mole) of $LiAlH(O\text{-}t\text{-}Bu)_3$ in 160 ml of dry bis(2-methoxyethyl)ether (diglyme) was cooled to -70° and a solution of 21.9 g (0.88 mole) of the acid chloride in 150 ml of diglyme was added drop-wise over 45 min. After addition was complete the stirred mixture was allowed to warm to room temp over 2 hr, and was then poured over 1200 g of crushed ice. The mixture was stirred vigorously and the pptd solid collected by filtration. The filter cake was extracted with 3 x 500 ml portions of abs EtOH and 2 x 400 ml $Et_2O$. The extracts were combined, taken to dryness, and the residue steam distilled. The solid was collected from the steam distillate and dried. Yield, 6.8 g (36%) mp 73-74.5° [lit (179) mp 74°]. ir (KBr) 1665 $cm^{-1}$ (C=O). nmr ($CCl_4$) δ3.98 (s, 3, $ArOCH_3$); δ7.14-7.84 (m, 3, ArH); δ9.80 (s, 1, CHO).

2-Bromo-4,5-dimethoxybenzaldehyde 46d. To a solution of 43.5 g (0.26 mole) of veratraldehyde in 200 ml $CH_2Cl_2$ was added 75 g (0.288 mole) of anhyd $SnCl_4$, followed by 42.3 g

(0.264 moles) of $Br_2$ over 0.5 hr. The resulting soln was stirred overnight at room temp and then poured over 150 g of ice. The organic layer was washed with 2 x 200 ml conc HCl, 2 x 100 ml $H_2O$, 100 ml 10% $NaHCO_3$, and then with water until the washings were neutral. The $CH_2Cl_2$ was dried ($Na_2SO_4$), removed in vacuo, and the crude solid recrystallized from MeOH-$H_2O$. Yield, 39 g (75%) mp 147° [lit (239) mp 147°]. ir (KBr) 1670 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ3.94 (s, 3, $ArOCH_3$); δ3.97 (s, 3, $ArOCH_3$); δ7.08 (s, 1, ArH); δ7.44 (s, 1, ArH); δ10.3 (s, 1, CHO).

3,5-Dimethoxy-4-bromobenzoic acid. To a soln of 60 g (1.5 mole) of NaOH in 400 ml of $H_2O$ was added 62 g (0.266 mole) of 3,5-dihydroxy-4-bromobenzoic acid (K & K Laboratories, Inc.). Dimethyl sulfate 89 g (0.71 mole) was added rapidly with vigorous stirring. The temp rose to 50°, the mixture was stirred 10 min, and a second portion of 89 g (0.71 mole) of $(CH_3)_2 SO_4$ was rapidly added and the temperature allowed to rise to 75°. The mixture was refluxed 1 hr, 15 g of NaOH was added and the refluxing continued 0.5 hr. The mixture was cooled, acidified with 6 N HCl, and the pptd solid collected by filtrn. The acid was recrystallized from EtOH-$H_2O$, mp 248-250° [lit (240) mp 249-250°]. Yield, 54 g (78%). ir (KBr) 3200-2500 $cm^{-1}$ (COOH); 1700 $cm^{-1}$ (C=O);

(Sadtler Standard Spectra, Midget edition, infrared spectrogram 42147). nmr (DMSO) δ3.98 (s, 6, $ArOCH_3$); δ7.26 (s, 2, ArH); (Sadtler nmr spectrum 13423M).

3,5-Dimethoxy-4-bromobenzaldehyde 46e. The procedure was identical to that for the preparation of 46c, but using 3,5-dimethoxy-4-bromobenzoyl chloride. The crude aldehyde was recrystallized from MeOH-$H_2O$, mp 112-114°. ir (KBr) 1700 $cm^{-1}$ (C=O); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42148). nmr ($CDCl_3$) δ3.99 (s, 6, $ArOCH_3$); δ7.07 (s, 2, ArH); δ9.92 (s, 1, CHO); (Sadtler nmr spectrum 13424M).

Anal. Calcd for $C_9H_9BrO_3$: C, 44.09; H, 3.70. Found: C, 44.20; H, 4.06.

2,5-Dimethoxy-4-bromobenzaldehyde 46f. To a solution of 66.5 g (0.4 mole) of 2,5-dimethoxybenzaldehyde (Eastman practical grade) in 300 ml $CH_2Cl_2$ was added 115 g (0.44 mole) of anhyd $SnCl_4$. Bromine, 64 g (0.40 mole) was added over 1 hr and the solution then heated to reflux for 2 hr and stirred overnight at room temp. The resultant orange suspension was poured over ice and extracted with water. The organic layer was washed with 10% $NaHCO_3$ soln and then with $H_2O$ until the water washes were neutral. The $CH_2Cl_2$ was removed in vacuo and the residue recrystallized from MeOH-$H_2O$, mp 132-133°. Yield 64 g (66%). ir (KBr) 1680

$cm^{-1}$ (C=O); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42154). nmr ($CDCl_3$) δ3.81 (s, 3, $ArOCH_3$); δ3.83 (s, 3, $ArOCH_3$); δ7.20 (s, 1, ArH); δ7.28 (s, 1, ArH); δ10.32 (s, 1, CHO); (Sadtler nmr spectrum 13427M). A small sample was oxidized with aqueous permanganate to the corresponding benzoic acid, mp 170° [lit (241) mp 170°].

Anal. Calcd for $C_9H_9BrO_3$: C, 44.09; H, 3.70. Found: C, 43.64; H, 3.46.

1-(2-Bromo-5-methoxyphenyl)-2-nitropropene 47a. Prepared by condensation of 46a with $EtNO_2$ in acetic acid contg ammonium acetate according to the method of Gairaud and Lappin (181). The crude nitrocompound was recryst from MeOH. Yield 61.8%, mp 58-59.5°. ir (melt) (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42142). nmr ($CDCl_3$) δ2.31 (s, 3, $CH_3$); δ3.81 (s, 3, $ArOCH_3$); δ6.73-7.0 (m, 2, ArH); δ7.4-7.7 (m, 1, ArH); δ8.04 (s, 1, ArC<u>H</u>=); (Sadtler nmr spectrum 13420M).

Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.13; H, 3.67; N, 5.14. Found: C, 44.07; H, 3.78; N, 4.92.

1-(3-Bromo-4-methoxyphenyl)-2-nitropene 47b. Prepared from 46b in a manner identical to 47a. Yield 45%. Mp 73-74°. ir (film) (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42156). nmr ($CDCl_3$) δ2.41 (s, 3, $CH_3$); δ3.91 (s, 3, $ArOCH_3$); δ6.9-7.6 (m, 3, ArH); δ7.90 (s, 1, ArC<u>H</u>=); (Sadtler nmr spectrum 13428M).

Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.13; H, 3.67; N, 5.14. Found: C, 43.71; H, 3.76; N, 4.82.

1-(3-Methoxy-4-bromophenyl)-2-nitropropene 47c. Prepared from 46c in a manner identical to 47a. Yield, 36.8%. mp 66.5-67°. ir (melt) (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42150). nmr ($CCl_4$) δ2.42 (s, 3, $CH_3$); δ3.94 (s, 3, $ArOCH_3$); δ6.7-7.0 (m, 2, ArH); δ7.5-7.67 (2s, 1, ArH); δ7.95 (s, 1, ArCH=).

Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.13; H, 3.67; N, 5.14. Found: C, 44.45; H, 3.56; N, 4.94.

1-(2-Bromo-4,5-dimethoxyphenyl)-2-nitropropene 47d. Prepared from 46d in a manner identical to 47a. Yield, 59.4%. mp 105-106°. ir (KBr) (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42158). nmr ($CDCl_3$) δ2.37 (s, 3, $CH_3$); δ3.88 (s, 3, $ArOCH_3$); δ3.90 (s, 3, $ArOCH_3$); δ6.83 (s, 1, ArH); δ7.11 (s, 1, ArH); δ8.10 (s, 1, ArCH=); (Sadtler nmr spectrum 13431M).

Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.72; H, 3.97; N, 4.63. Found: C, 43.43; H, 4.35; N, 4.24.

1-(3,5-Dimethoxy-4-bromophenyl)-2-nitropropene 47e. Prepared from 46e in a manner identical to 47a. Yield, 46.8%. mp 121-121.5°. ir (KBr) (Sadtler Standard Spectra, Midget

edition, infrared spectrogram 42146). nmr ($CDCl_3$) δ2.47 (s, 3, $CH_3$); δ3.95 (s, 6, $ArOCH_3$); δ6.64 (s, 2, ArH); δ8.05 (s, 1, ArCH=).

Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.72; H, 3.97; N, 4.63. Found: C, 44.03; H, 3.87; N, 4.46.

1-(2,5-Dimethoxy-4-bromophenyl)-2-nitropropene 47f. Prepared from 46f in a manner identical to 47a. Yield, 57%. Mp 113.5-115°. ir (KBr) (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42153). nmr ($CDCl_3$) δ2.38 (s, 3, $CH_3$); δ3.81 (s, 3, $ArOCH_3$); δ3.84 (s, 3, $ArOCH_3$); δ6.84 (s, 1, ArH); δ7.13 (s, 1, ArH); δ8.11 (s, 1, ArCH=); (Sadtler nmr spectrum 13426M).

Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.72; H, 3.97; N, 4.63. Found: C, 43.50; H, 4.07; N, 4.40.

2-Bromo-5-methoxyphenylisopropylamine 43a. A solution of 2.72 g (0.01 mole) of 47a was dissolved in 100 ml of anhyd diethyl ether and added to a -80° (solid $CO_2$-acetone bath) solution of 0.758 g (0.02 mole) LAH in 40 ml dry ether. After addition was complete the stirred solution was removed from the cooling bath and allowed to warm to room temperature and stirred overnight. The complex was decomposed by careful addition of 5 ml of $H_2O$, the precipitated alumina was filtered out and the ether filtrate was taken to dryness. The residue was taken up in abs EtOH and neutralized

with 6 N HCl. The hydrochloride was taken to dryness from ethanol-benzene several times and then repeatedly recrystallized from isopropanol-ether. Yield, 20%. Mp 151.5-153°. ir (KBr) 2950 $cm^{-1}$ ($-NH_3^+$); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42141). nmr (DMSO) δ1.20 (d, 3, $CH_3$); δ3.07 (m, 2, $-CH_2-$); δ3.48 (m, 1, -CH-); δ3.80 (s, 3, $ArOCH_3$); δ6.74-7.17 (m, 2, ArH); δ7.48, 7.65 (2s, 1, ArH); δ8.50 (s, 3, $-NH_3^+$).

Anal. Calcd for $C_{10}H_{15}BrClNO$: C, 42.80; H, 5.38; N, 4.99. Found: C, 42.63; H, 5.42; N, 4.73.

3-Bromo-4-methoxyphenylisopropylamine 43b. Prepared from 47b in a manner identical to 43a. Yield, 29%. Mp 210-213°. ir (KBr) 3100 $cm^{-1}$ ($NH_3^+$); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42155). nmr ($D_2O$) δ1.42 (d, 3, $CH_3$); δ2.68-3.40 (m, 2, $-CH_2-$); δ3.73 (m, 1, -CH-); δ3.97 (s, 3, $ArOCH_3$); δ7.1-7.56 (m, 3, ArH); (Sadtler nmr spectrum 13428M).

Anal. Calcd for $C_{10}H_{15}BrClNO$: C, 42.80; H, 5.38; N, 4.99. Found: C, 42.43; H, 5.46; N, 4.66.

3-Methoxy-4-bromophenylisopropylamine 43c. Prepared from 47c in a manner identical to 43a. Yield, 32%. Mp 161.5-163°. ir (KBr) 2969 $cm^{-1}$ ($NH_3^+$); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42149). nmr ($D_2O$)

δ1.42 (d, 3, $CH_3$); δ3.03 (m, 2, $-CH_2-$); δ3.72 (m, 1, -CH-); δ4.01 (s, 3, $ArOCH_3$); δ6.8-7.22 (m, 2, ArH); δ7.55, 7.70 (2s, 1, ArH).

Anal. Calcd for $C_{10}H_{15}BrClNO$: C, 42.80; H, 5.38; N, 4.99. Found: C, 42.76; H, 5.31; N, 4.97.

2-Bromo-4,5-dimethoxyphenylisopropylamine 43d. Prepared from 47d in a manner identical to 43a. Yield, 42%. Mp 214-215.5°. ir (KBr) 2950 $cm^{-1}$ ($NH_3^+$); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42157). nmr ($D_2O$) δ1.43 (d, 3, $CH_3$); δ3.77 (m, 1, -CH-); δ3.89 (s, 3, $ArOCH_3$); δ3.92 (s, 3, $ArOCH_3$); δ7.00 (s, 1, ArH); δ7.16 (s, 1, ArH); (Sadtler nmr spectrum 13430M).

Anal. Calcd for $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.51; N, 4.51. Found: C, 42.93; H, 5.85; N, 4.41.

3,5-Dimethoxy-4-bromophenylisopropylamine 43e. Prepared from 47e in a manner identical to 43a. Yield, 36.8%. Mp 221-222°. ir (KBr) 2960 $cm^{-1}$ ($NH_3^+$); (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42145). nmr (DMSO) δ1.20 (d, 3, $CH_3$); δ2.88 (t, 2, $CH_2$); δ3.4 (m, 1, -CH-); δ3.88 (s, 6, $OCH_3$); δ6.73 (s, 2, ArH); δ8.34 (s, 3, $NH_3^+$).

Anal. Calcd for $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.51; N, 4.51. Found: C, 42.36; H, 5.38; N, 4.44.

2,5-Dimethoxy-4-bromophenylisopropylamine 43f. Prepared from 47f in a manner identical to 43a. Yield, 29.5%. Mp 198-199°. ir (KBr) 2950 $cm^{-1}$ (Sadtler Standard Spectra, Midget edition, infrared spectrogram 42152). nmr ($D_2O$) δ1.40 (d, 3, $CH_3$); δ3.03 (t, 2, $CH_2$); δ3.79 (m, 1, -CH-); δ3.89 (s, 3, $OCH_3$); δ3.91 (s, 3, $OCH_3$); δ7.06 (s, 1, ArH); δ7.21 (s, 1, ArH); (Sadtler nmr spectrum 13680M).

Anal. Calcd for $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.51; N, 4.51. Found: C, 42.32; H, 5.66; N, 4.29.

[R;R]-(+)-N-(α-phenethyl)-phenylisopropylamine HCl 49a. Phenylacetone, 6.71 g (0.05 mole) (Matheson, Coleman, and Bell) and 6.06 g (0.05 mole) of (+)-α-methylbenzylamine (Aldrich) were refluxed together in 50 ml of benzene for 24 hr with continuous water removal. The benzene was removed and the residue dissolved in 50 ml of absolute ethanol and shaken over 2 g of ethanol-washed W-2 Raney nickel in a 500 ml Parr bottle at 50 psig hydrogen pressure. The theoretical amount of hydrogen was absorbed in 24 hr and the mixture was filtered through sintered glass and the filtrate acidified with 2N HCl-ethanol. The solvent was removed in vacuo and the residue diluted in diethyl ether. The HCl salt precipitated and was recrystallized from acetone-isopropanol, mp 233.5-234.5°. Yield, 70.5%. $[\alpha]_D$ = +21.0° (c = 2; MeOH).

Anal. Calcd for $C_{17}H_{22}ClN$: C, 74.02; H, 8.03; N, 4.08. Found: C, 73.80; H, 8.20; N, 4.95.

[S;S]-(-)-3,4-Dimethoxy-N-(α-phenethyl)-phenylisopropylamine hydrochloride 49b. Prepared from 3,4-dimethoxyphenylacetone (RESEARCH Organic/Inorganic Chemical Corp., Sun Valley, Calif.) and (-)-α-methylbenzylamine in a manner identical to 49a. Yield, 48%. Mp 216-217° [lit (185) mp 216-217°]. $[\alpha]_D$ = -20.5° (c = 2; MeOH) [lit (185) $[\alpha]_D$ = -20.5°].

[R;R]-(+)-2,3-Dimethoxy-N-(α-phenethyl)-phenylisopropylamine hydrochloride 49c. Prepared from 2,3-dimethoxyphenylacetone (242) and (+)α-methylbenzylamine in a manner identical to 49a. Yield, 32%. Mp 181-182°. $[\alpha]_D$ = +22.1° (c = 2; MeOH).

Anal. Calcd for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17. Found: C, 68.33; H, 8.14; N, 3.80.

[S;S]-(-)-2,3-Dimethoxy-N-(α-phenethyl)-phenylisopropylamine hydrochloride 49d. Prepared from 2,3-dimethoxyphenylacetone and (-)-α-methylbenzylamine in a manner identical to 49a. Yield, 12% (the phenylacetone was an old sample which after distillation was used for the preparation of 49c, yield, 32%). Mp 180-181°. $[\alpha]_D$ = -21.7° (c = 2; MeOH).

Anal. Calcd for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17. Found: C, 68.13; H, 8.08; N, 4.14.

[R;R]-(+)-2,5-Dimethoxy-N-(α-phenethyl)-phenylisopropylamine hydrochloride 49e. Prepared from 2,5-dimethoxyphenylacetone (RESEARCH Organic/Inorganic Chemical Corp., Sun Valley, Calif.) and (+)-α-methylbenzylamine in a manner identical to 49a. Yield, 63%. Mp 227-228°. $[\alpha]_D$ = +7.50° (c = 2; MeOH).

Anal. Calcd for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.94; H, 8.02; N, 3.80.

[S;S]-(-)-2,5-Dimethoxy-N-(α-phenethyl)-phenylisopropylamine hydrochloride 49f. Prepared from 2,5-dimethoxyphenylacetone and (-)-α-methylbenzylamine in a manner identical to 49a. Yield, 67%. Mp 227-228°. $[\alpha]_D$ = -7.75° (c = 2; MeOH).

Anal. Calcd for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.80; N, 4.17. Found: C, 68.13; H, 8.02; N, 3.91.

(-)-Phenylisopropylamine hydrochloride 50a. To a slurry of 0.35 g 10% Pd-C in 5 ml of $H_2O$ was added a solution of 5 g of 49a in 90 ml of methanol. The mixture was shaken in a 500 ml Parr bottle at 50 psig hydrogen pressure for 48 hr. The catalyst was removed by filtration and the solvent removed in vacuo. A quantitative yield of material melting at 148-154° was obtained. One recrystallization from isopropanol-ether gave mp 157-158°. Yield, 2.76 g (83%). $[\alpha]_D$ = -27.2° (c = 2; $H_2O$) [lit (243) $[\alpha]_D$ = 24.8°].

(+)-3,4-Dimethoxyphenylisopropylamine hydrochloride 50b. Prepared from 49b in a manner identical to 50a. Yield, 90%. Mp 141-142° [lit (185) mp 141-142°]. $[\alpha]_D$ = +23.1° (c = 2; $H_2O$) [lit (130) $[\alpha]_D$ = +23.0°].

(-)-2,3-Dimethoxyphenylisopropylamine hydrochloride 50c. Prepared from 49c in a manner identical to 50a. Yield, 92%. Mp 124-125°. $[\alpha]_D$ = -16.9° (c = 2; $H_2O$).

Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 59.48; H, 8.30; N, 6.99.

(+)-2,3-Dimethoxyphenylisopropylamine hydrochloride 50d. Prepared from 49d in a manner identical to 50a. Yield, 90%. Mp 123-124°. $[\alpha]_D$ = +16.6° (c = 2; $H_2O$).

Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 57.06; H, 8.09; N, 6.41.

(-)-2,5-Dimethoxyphenylisopropylamine hydrochloride 50e. Prepared from 49e in a manner identical to 50a. Yield, 87%. Mp 145-146°. $[\alpha]_D$ = -18.7° (c = 2; $H_2O$).

Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 56.79; H, 8.10; N, 5.75.

(+)-2,5-Dimethoxyphenylisopropylamine hydrochloride 50f. Prepared from 49f in a manner identical to 50a. Yield, 90%. Mp 144-145°. $[\alpha]_D$ = +18.0° (c = 2; $H_2O$).

Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 56.91; H, 8.03; N, 6.19.

(-)-2,5-Dimethoxy-4-bromophenylisopropylamine hydrochloride 43f. Prepared by a modification of the method of Harley-Mason (163), 1.62 g (8.3 millimole) of 50e, as the free amine, was dissolved in 6 ml of acetic acid. A solution of 1.33 g (8.3 millimole) of bromine in 4.5 ml of acetic acid was added to the amine solution over 10 min. The resulting orange solution was stirred 24 hr at room temp. The mixture was diluted with 200 ml of ether and allowed to stand at 5° for several hours. The precipitated hydrobromide salt was collected by filtration, neutralized to the free base with excess 10% sodium hydroxide solution, then taken up into ether and precipitated with dry HCl as the hydrochloride salt. The salt was recrystallized from isopropanol, mp 203.5-204°. Yield, 1.40 g (54.5%). $[\alpha]_D$ = -13.7° (c = 2; $H_2O$).

Anal. Calcd for $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.51; N, 4.51. Found: C, 42.13; H, 5.64; N, 4.14.

(+)-2,5-Dimethoxy-4-bromophenylisopropylamine hydrochloride 43f. Prepared from 50f exactly as described for (-)-43f. Yield, 54.5%. Mp 204-205°. $[\alpha]_D$ = +13.7° (c = 2; $H_2O$).

Anal. Calcd for $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.51; N, 4.51. Found: C, 42.25; H, 5.72; N, 4.28.

Glc Analysis of enantiomeric purity with MTPA amides. Following the method of Dale, et al (188), 1 gram (4.27 millimole) of (+) or (-) α-methoxy-α-trifluoromethyl phenylacetic acid (MTPA; Aldrich) was refluxed 12 hr with 5 ml thionyl chloride. The $SOCl_2$ was removed under reduced pressure and the MTPA-Cl diluted with 1 ml dry pyridine and 4.6 ml $CHCl_3$. 0.5 Millimoles of one of the phenylisopropylamine hydrochlorides was dissolved in 0.25 ml pyridine and 0.5 ml $CHCl_3$ and allowed to sit with one-fourth of the MTPA-Cl solution (1.06 millimole) overnight. The solution was then diluted to 10 ml with $CHCl_3$ and washed with 3N HCl, 5% $NaHCO_3$ solution, and $H_2O$. The $CHCl_3$ was dried ($Na_2SO_4$) and removed at reduced pressure. The resulting viscous amide was analyzed directly.

Glc Analysis of MTPA amides. Copper column, 1.33 m x 3.18 mm i.d., packed with 2% Carbowax 20M on 80-100 mesh Gas Chrom Q (Applied Science Labs). The column was conditioned for 24 hr at 225° before use and operated at the same temp. The He carrier gas flow was adjusted to ca 100 ml/min. Sample and detector temperatures were set at 300°. Solutions containing 5-10 μg of the MTPA amides were injected and the per cent composition determined by cutting out the peaks and integrating the area by direct weighing. Results of the analysis are given below:

| Compound | Enantiomeric Purity |
|---|---|
| 50b | 97% |
| 50c | 97% |
| 50e | 96% |
| 50f | 96% |

Preparation of N-trifluoroacetyl-S-prolylamides and determination of absolute configuration. N-Trifluoroacetyl-S-prolyl chloride was prepared by the method of Wells (190). One gram (8.7 mm) of l-proline (Sigma Chemical Co.) in a 125 ml flask was swirled with 5 g trifluoroacetic anhydride until all the solid had dissolved. The excess trifluoroacetic anhydride was evaporated under a stream of dry nitrogen. Five ml of $SOCl_2$ was added and the solution allowed to stand for 2 hr and excess $SOCl_2$ was evaporated under a stream of dry nitrogen. The chloride was taken up in 2 ml dry pyridine and 9.2 ml $CHCl_3$. 0.5 Millimoles of one of the phenylisopropylamine hydrochlorides was dissolved in 0.25 ml pyridine and 0.5 ml $CHCl_3$ and allowed to sit with one-fourth of the trifluoroacetyl-S-prolyl chloride solution (2.15 millimoles). The solution was allowed to stand overnight and then worked-up identically to the MTPA amide procedure detailed above. Glc analysis was carried out using the same column and conditions as was described for the

MTPA amides. Order of elution of the various enantiomers prepared above confirmed that they all possessed the R-(-) and S-(+) absolute configurations.

## Part II.

Methyl 3-(2,5-dimethoxy-4-methylbenzoyl)-propionate 52. 2,5-Dimethoxytoluene (Eastman practical grade) 76.1 g (0.5 mole), and 77.8 g (0.5 mole) of 3-carbomethoxypropionyl chloride were dissolved in 1500 ml of dry methylene chloride and cooled to 0°. Stannic chloride (anhydrous) 286 g (1.10 mole) was added and the mixture was stirred for 3.5 hr in an ice-$H_2O$ bath. The mixture was poured over 2 l of ice-water and the organic layer separated, and then washed with 500 ml 10% HCl, 2 x 500 ml 5% $NaHCO_3$, 2 x 500 ml $H_2O$ and dried ($Na_2SO_4$). The methylene chloride was removed under reduced pressure and the residue taken up into hot diethyl ether and crystallized by cooling. Yield, 106.5 g (80%). Mp 86-86.5°. ir (KBr) 1730 $cm^{-1}$ (C=O); 1655 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.26 (s, 3, $ArCH_3$); δ2.43 (t, 2, $-CH_2-$); δ3.10 (t, 2, $-CH_2-$); δ3.72 (s, 3, $COOCH_3$); δ3.84 (s, 3, $ArOCH_3$); δ3.90 (s, 3, $ArOCH_3$); δ6.83 (s, 1, ArH); δ7.37 (s, 1, ArH).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.13; H, 6.92.

Methyl 3-bromo-3-(2,5-dimethoxy-4-methylbenzoyl)-propionate 53. By a modification of the method of Wilds (217), 26.6 g (0.1mole) of 52 was dissolved in 300 ml of a 1:1 ether-chloroform mixture and cooled to 5°. Bromine 15.98 g (0.1 mole) was added dropwise over 0.5 hr. The ice-bath was removed and stirring continued for 2 hr. The reaction mixture was washed with water until the washings were neutral and the organic phase dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue crystallized from hexane, mp 67-68°. Yield 29.3 g (85%). ir (KBr) 1725 $cm^{-1}$ (C=O); 1655 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.28 (s, 3, $ArCH_3$); δ3.23 (q of d's, 2, $CH_2$); δ3.72 (s, 3, $COOCH_3$); δ3.84 (s, 3, $ArOCH_3$); δ3.94 (s, 3, $ArOCH_3$); δ5.90 (t, 1, -CH-); δ6.84 (s, 1, ArH); δ7.35 (s, 1, ArH).

Anal. Calcd for $C_{14}H_{17}BrO_5$: C, 48.71; H, 4.96. Found: C, 48.39; H, 4.89.

Methyl 3-nitro-3-(2,5-dimethoxy-4-methylbenzoyl)-propionate 54. Based on the method of Kornblum, et al (212), 24.1 g (0.07 mole) of 53 was added to a stirring solution of 9.65 g (0.14 mole) of $NaNO_2$ and 12.15 g (0.075 mole) of phloroglucinol in 95 ml of dry DMSO. The mixture was stirred for 3 hr then poured into 1,000 ml of water. The precipitated yellow solid was collected by filtration and recrystallized from MeOH, mp 127-128.5°. ir (KBr) 1730 $cm^{-1}$ (C=O); 1660 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.30 (s, 3, $ArCH_3$); δ3.23 (q of

of d's, 2, $CH_2$); δ3.72 (s, 3, $COOCH_3$); δ3.85 (s, 3, $ArOCH_3$); δ3.90 (s, 3, $ArOCH_3$); δ6.62 (q of d's, 1, -CH-); δ6.88 (s, 1, ArH); δ7.44 (s, 1, ArH).

Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.08; H, 5.57; N, 4.10.

Methyl 4-hydroxy-4-(2,5-dimethoxy-4-methylphenyl)-3-nitrobutyrate 55. The nitroketone 54 12.44 g (0.04 mole) was suspended in 200 ml of methanol and cooled to 10°. $NaBH_4$, 1.0 g (26.4 millimole) was added and the mixture stirred at 5-10° for 2 hr. The methanolic solution was then poured into 1600 ml of ice-cold saturated NaCl solution and the pH adjusted to 4. The precipitate was collected by filtration and washed on the filter with water and then air dried. Yield, 8.3 g (67.2%). An analytical sample was recryst from MeOH. Mp 128° and 142° (erythro and threo isomer mixture). ir (KBr) 3460 $cm^{-1}$ (OH); 1735 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.22 (s, 3, $ArCH_3$); δ3.40 (m, 1, OH); δ3.61 (s, 3, $COOCH_3$); δ3.80 (s, 3, $ArOCH_3$); δ3.85 (s, 3, $ArOCH_3$); δ5.22 (m, 2, -CH-); δ6.79 (s, 2, ArH).

Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.38; N, 4.47. Found: C, 54.10; H, 6.38; N, 4.73.

Catalytic reduction of 55. The nitroalcohol 55, 3.13 g (0.01 mole) was dissolved in 150 ml methanol containing 100 mg of 10% Pd-C. Sulfuric acid, 0.2 ml, was added and the

mixture shaken at room temp in a 500 ml Parr bottle at 50 psig hydrogen pressure. No hydrogen was taken up in 1 hr and a further 1.0 ml of $H_2SO_4$ was added and shaking was continued for 24 hr. At this time 0.01 mole of $H_2$ had been absorbed. The catalyst was removed by filtration and the filtrate reduced to a syrup under reduced pressure. The residue was dissolved in cold $H_2O$ and extracted with ether. The ether extract was reduced to dryness and the residue identified by ir and melting point to be unreduced 55. The acidic aqueous solution was then made basic with $K_2CO_3$ and extracted with ether. Dry HCl was added to the ether extract whereupon the HCl salt precipitated. The crude HCl salt weighed 500 mg. ir (KBr) 3350 $cm^{-1}$ (OH); 2900 $cm^{-1}$ (broad, $NH_3^+$); 1740 $cm^{-1}$ (C=O); 1770 $cm^{-1}$ (C=O). The mixture of products was not further characterized.

Methyl 3-N-methylbenzylamino-3-(2,5-dimethoxy-4-methylbenzyl)-propionate 65. A solution of 68.98 g (0.20 mole) of 53 in 600 ml of dry benzene was stirred at room temperature under nitrogen and 48.5 g (0.40 mole) of N-methylbenzylamine was added rapidly. A precipitate formed within 2-3 min and the mixture was stirred 30 min and then heated to reflux (under $N_2$) for 4 hr. The mixture was cooled and the HBr salt of the excess amine removed by filtration (40.2 g, 99.3% of the bromine removed). The filtrate was reduced in vacuo and the residual oil crystallized from ether-hexane.

The crude solid was recrystallized from ether-hexane to give mp 65.5-66.5°. Yield, 53 g (70%). ir (KBr) 1720 $cm^{-1}$ (C=O); 1652 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.25 (s, 3, N-$CH_3$); δ2.28 (s, 3, Ar$CH_3$); δ3.77 (m, 5, -CH-; $CH_2$); δ3.77 (s, 3, $COOCH_3$); δ3.80 (s, 3, Ar$OCH_3$); δ3.84 (s, 3, Ar$OCH_3$); δ6.77 (s, 1, ArH); δ7.27 (s, 6, ArH).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.50; H, 7.01; N, 3.64. Found: C, 68.63; H, 7.17; N, 3.24.

Formylation of 3-methoxytoluene, 81. Using a modification of the method of Rieche, et al (200), 55.0 g (0.45 mole) of 3-methoxytoluene was dissolved in 600 ml of methylene chloride and cooled to 10°. Anhydrous $SnCl_4$, 234 g (0.90 mole) was added, followed by 77.5 g (0.675 mole) of dichloromethyl methyl ether, added over 50 min, while maintaining the temperature at 5-10°. The solution was allowed to warm to room temperature and refluxed until HCl evolution ceased (2hr). The mixture was poured over 150 g of ice, the organic layer separated and then washed with 2 x 300 ml 3N HCl, then 2 x 250 ml $H_2O$. The solvent was removed in vacuo and the residue shaken with a saturated solution of sodium bisulfite. The resulting solid was collected by filtration, dissolved in water and the aqueous solution washed several times with ether. The aqueous bisulfite addition product solution was added to a warm 10% solution of sodium carbonate. The basic solution was then extracted with ether, the ether extracts

dried ($Na_2SO_4$) and the ether removed under reduced pressure. The residue was vacuum distilled, bp 67-8°/0.25 mm Hg. Tlc (silica gel-benzene) followed by detection with 2,4-DNP spray revealed two spots of $R_f$ = 0.41 and 0.47. ir (neat) 1680 $cm^{-1}$; 1685 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.42; δ2.58; δ2.65 (3s, 3, $ArCH_3$); δ3.60, δ3.62, δ3.65 (3s, 3, $ArOCH_3$); δ6.67-7.9 (m, 3, ArH); δ10.15, δ10.43, δ10.70 (3s, 1, CHO).

Acetylation of 3-methoxytoluene, 81. Meta-methoxytoluene, 97.6 g (0.80 mole) and 62.8 g (0.8 mole) of acetyl chloride were dissolved in 800 ml dry methylene chloride and cooled to 0°. Anhydrous $SnCl_4$, 208 g (0.44 mole) was slowly added over 1 hr, maintaining the temperature at 5-10°. The ice bath was then removed and the mixture allowed to warm to 25° and then heated to reflux for 6 hr. The mixture was cooled and poured over 130 g of ice. The aqueous layer was discarded and the organic phase washed with 2 x 250 ml 3N HCl, 2 x 500 ml $H_2O$, and dried ($Na_2SO_4$). The solvent was removed in vacuo and the residue vacuum distilled, bp 83-85°/0.20 mm Hg. Yield, 120 g (91.5%). Tlc analysis revealed two spots of $R_f$ = 0.30 and 0.36 (silica gel-ether). ir (neat) 1670 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.38, δ2.55, δ2.57, δ2.60 (4s, 6, $CH_3$); δ3.85, δ3.90 (2s, 3, $ArOCH_3$); δ6.79, δ7.75 (2m, 3, ArH).

2-Methoxy-5-hydroxy-p-tolualdehyde 86. Prepared by the method of Rieche, et al,(200) 13.8 g (100 millimole) of 4-methoxy-o-cresol 71 was dissolved in 150 ml of dry methylene chloride, cooled to 10°, and 37.9 g (200 millimole) of anhydrous $TiCl_4$ added. Dichloromethyl methyl ether, 19 g (165 millimole) was added over 30 min, keeping the temperature at 5-10°. The mixture was stirred for 1 hr, then allowed to warm to room temperature and heated to reflux for 1 hr (until HCl evolution ceased). The solution was cooled and poured over 100 g of ice. The aqueous layer was separated and discarded and the organic phase washed with 2 x 50 ml 6N HCl and 2 x 100 ml $H_2O$. The solvent was removed in vacuo and the tarry residue extracted repeatedly with 10% $NaHSO_3$ solution. The bisulfite solution was washed with ether and then decomposed by pouring into saturated sodium carbonate solution. The solid material was collected by filtration, washed on the filter with water, and recrystallized from ethanol-water, mp 136°. Yield 7.5 g (45%). ir (KBr) 3470 $cm^{-1}$ (OH); 1670 $cm^{-1}$ (C=O). nmr (DMSO) $\delta$2.25 (s, 3, $ArCH_3$); $\delta$3.87 (s, 3, $ArOCH_3$); $\delta$7.05 (s, 1, ArH); $\delta$7.17 (s, 1, ArH); $\delta$9.31 (s, 1, OH); $\delta$10.30 (s, 1, CHO).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.28; H, 6.23.

A sample was O-methylated by methyl iodide and $K_2CO_3$ in dry acetone and gave, after recrystn from MeOH-$H_2O$,

material with mp 84-86° [lit (197) mp 85-86° for 2,5-dimethoxy-4-methylbenzaldehyde]. The nmr spectrum was identical to that of authentic 2,5-dimethoxy-4-methylbenzaldehyde.

2,6-Di-(hydroxymethyl)-4-methoxyphenol 88. By a modification of the method of Moran, et al,(204) para-methoxy phenol, 339 g (2.73 mole), 461 g (ca. 5.7 mole) of 37% formalin solution, and 79 g (1.41 mole) of CaO in 3,000 ml of $H_2O$ were stirred together 42 hr under nitrogen at room temperature. The resulting yellow slurry was acidified to pH 3 with approximately 140 g of acetic acid, then, while maintaining a nitrogen purge, was heated on the steam bath with stirring until all solid had dissolved. The stirrer was stopped and the solution allowed to cool to room temperature, cooled, and stored 12 hr at 5°. The crystals were collected by vacuum filtration. Yield, 315 g (62.7%). Mp 127-8° [lit (204) mp 127-8°]. ir (KBr) 3200-3350 $cm^{-1}$ broad (OH). nmr (DMSO) $\delta$3.72 (s, 3, $OCH_3$); $\delta$4.40 (s, 4, $CH_2$); $\delta$6.13 (s, 3, OH); $\delta$6.79 (s, 2, ArH).

Catalytic reduction of 88. A solution of 184 g (1.0 mole) of 88 in 1,000 ml of 95% ethanol was warmed to 50° and 1.5 ml of concentrated $H_2SO_4$ added. The mixture was shaken over 2.0 g of 10% Pd-C in a 2 liter Parr bottle at 50 psig. The reduction was stopped at 3.5 hr, at which time 1.0 mole

of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate was stirred with solid $NaHCO_3$ until the alcoholic solution was no longer acidic. (Failure to completely neutralize the acid at this point results in complete decomposition of the reduction products, probably by a polymerization reaction.) The neutral solution was then filtered. Tlc analysis (silica-gel-ether) showed three components of $R_f$ = 0.66, 0.62, and 0.35. The two slower moving components had $R_f$ values identical to authentic 72 prepared by the method of Sayigh, et al,(197) and to unreduced starting material, 88, respectively. The solvent was removed in vacuo and the residual mass used directly in the next step.

2,5-Dimethoxy-3-methylbenzyl alcohol 73. The total residue from the reduction of 88 was dissolved in 250 ml of dry acetone. Methyl iodide, 153 g (1.08 mole) and 141 g (1.02 mole) of anhyd $K_2CO_3$ were added and the mixture was stirred and heated to reflux for 48 hr. The reaction was cooled, filtered, the ethanol removed in vacuo, and the residue taken up into ether. The ether solution was filtered, washed with 10% NaOH to remove unalkylated phenolic products, then washed with water until the washings were neutral. The ether was dried ($Na_2SO_4$), removed, and the residual oil vacuum distilled. The fraction was collected with

bp 94-96°/0.1 mm Hg [lit (197) bp 109-116°/0.6 mm]. Yield, 83.6 g (45.5% based on 88). The thin-layer chromatographic mobility ($R_f$ = 0.22 silica-gel-ether), ir and nmr spectra of this material were identical to those of 73 prepared by the method of Sayigh, et al (197). ir (neat) 3440 $cm^{-1}$ broad, (OH). nmr ($CDCl_3$) δ2.27 (s, 3, $CH_3$); δ2.40 (s, 1, OH); δ3.74 (s, 3, $ArOCH_3$); δ3.77 (s, 3, $ArOCH_3$); δ4.68 (s, 2, $CH_2$); δ6.70 (m, 2, ArH).

The forerun from the distillation was identified as 2,5-dimethoxy-m-xylene, bp 74-76°/0.1 mm Hg [lit (204) bp 103°/10 mm Hg], $R_f$ = 0.73 (tlc, silica gel-ether). nmr ($CDCl_3$) δ2.25 (s, 6, $CH_3$); δ3.68 (s, 3, $ArOCH_3$); δ3.75 (s, 3, $ArOCH_3$); δ6.57 (s, 2, ArH).

The pot residue was identified as 2,6-di-(hydroxymethyl)-4-methoxyanisole, mp 112° [lit (204) mp 112°], $R_f$ = 0.03 (tlc, silica gel-ether). nmr (DMSO) δ3.64 (s, 3, $ArOCH_3$); δ3.72 (s, 3, $ArOCH_3$); δ4.52 (d, 4, $CH_2$); δ5.07 (t, 1, OH); δ6.90 (s, 2, ArH).

2,5-Dimethoxy-3-methylbenzaldehyde 67a. To a solution of 54.6 g (0.30 mole) of 73 in 500 ml of dry benzene, 173.9 g (2.0 M) of activated $MnO_2$ (Winthrop Special Chemicals Div.) was added. The mixture was refluxed and stirred overnight maintaining continuous water removal with a Dean-Stark tube (12.5 ml of $H_2O$ collected). The $MnO_2$ was removed by filtration (celite), and the bezene distilled off under reduced

pressure. The residue was recrystallized from hexane, mp 42.5-43° [lit (197) mp 40-41°]. Yield, 45.1 g (83.5%). The ir and nmr spectral properties were identical to a sample of 67a prepared by the method of Sayigh, et al (197). ir (film) 1690 $cm^{-1}$ (C=O); 1609 $cm^{-1}$ (C=C). nmr ($CDCl_3$) δ2.32 (s, 3, $ArCH_3$); δ3.82 (s, 3, $ArOCH_3$); δ3.87 (s, 3, $ArOCH_3$); δ7.12 (d of d's, 2, ArH); δ10.40 (s, 1, CHO).

2,5-Dimethoxy-3-methylcinnamic acid 74. The aldehyde 67a 79.2 g (0.44 mole), 95.5 g (0.82 mole) of malonic acid, 190 ml of pyridine, and 3.6 ml of piperidine were heated on the steam bath for 2.5 hr. The mixture was cooled and poured with stirring into a mixture of 300 ml conc HCl and 1200 ml of ice-water. The solid was collected by filtration and recrystallized from ethanol-water, mp 166-167°. Yield, 94.7 g (97%). ir (KBr) 2500-3000 $cm^{-1}$ (COOH); 1680 $cm^{-1}$ (C=O); 1600 $cm^{-1}$ broad (C=C). nmr (DMSO) δ2.25 (s, 3, $ArCH_3$); δ3.67 (s, 3, $ArOCH_3$); δ3.78 (s, 3, $ArOCH_3$); δ6.59 (d, 1, =CH); δ7.02 (d of d, 2, ArH); δ7.80 (d, 1, -CH); δ12.45 (s, 1, COOH).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.52; H, 6.37.

3-(2,5-Dimethoxy-3-methylphenyl)-propionic acid 75. The cinnamic acid 74, 44.5 g (0.02 mole), was dissolved in 800 ml of 95% ethanol and shaken over 2 g of 10% Pd-C at 40 psig

hydrogen pressure. The theoretical amount of hydrogen was taken up in less than 1 hr. The catalyst was removed by filtration and the residue recrystallized from benzene-hexane, mp 87.5-88.5°. Yield 44.1 g (98.2%). ir (KBr) 2700-3100 $cm^{-1}$ (COOH); 1700 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.27 (s, 3, $ArCH_3$); δ1.83-2.80 (m, 6, $CH_2$); δ3.67 (s, 3, $ArOCH_3$); δ3.74 (s, 3, $ArOCH_3$); δ6.57 (s, 2, ArH); δ10.60 (s, 1, (COOH).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.95; H, 7.25.

3-(2,5-Dimethoxy-3-methylphenyl)-propionyl chloride 76. The reduced acid 75, 22.4 g (0.10 mole) was dissolved in 80 ml of dry ether. Thionyl chloride, 53 ml, was added and the solution refluxed for 4.5 hr. The ether and excess $SOCl_2$ were removed *in vacuo* and the acid chloride vacuum distilled, bp 129-130°/1.0 mm Hg. ir (neat) 1790 $cm^{-1}$ (C=O). The acid chloride was not further characterized and was used directly in the next step.

Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.23. Found: C, 59.51; H, 6.42.

Methyl-4-(2,5-dimethoxy-3-methylphenyl)-butyrate 77. By the method of Elmore and King (195), 18.75 g (77.5 millimole) of the acid chloride 76 was slowly added, in two portions, to two 340 ml portions of an ethereal solution of

diazomethane, each portion containing 5.1 g (0.121 mole) of diazomethane. The solutions were allowed to sit overnight at room temperature and then the ether was removed under reduced pressure. The residual yellow oil was taken up into 180 ml of methanol, and a 10% solution of silver benzoate in triethylamine was added dropwise (207). Gas evolution began after addition of a few drops and the silver benzoate solution was added at a rate sufficient to maintain vigorous nitrogen evolution. After reaction had slowed considerably, the solution was refluxed 0.5 hr. After cooling, the mixture was filtered, and the methanol removed in vacuo. The residual oil was vacuum distilled, bp 122-124°/0.15 mm Hg. Yield, 17.1 g (88%). An analytical sample was crystallized as fine white needles from ether-hexane, mp 33-33.5°. ir (neat) 1738 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.26 (s, 3, $ArCH_3$); δ1.72-2.90 (m, 6, $CH_2$); δ3.68 (s, 6, $ArOCH_3$; $COOCH_3$); δ3.75 (s, 3, $ArOCH_3$); δ6.58 (s, 2, ArH).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.95; H, 8.38.

4-(2,5-Dimethoxy-3-methylphenyl)-butyric acid 78. Ester 77, 7.7 g (30 millimole), was refluxed 4 hr with a solution of 6 g of KOH pellets in 20 ml of water. The solution was cooled, acidified with conc HCl, and extracted several times with ether. The ether was dried ($Na_2SO_4$), removed under

reduced pressure, and the residue recrystallized from ether-hexane, mp 39.5-40.5°. Yield, 6.93 g (97%). ir (KBr) 2700-3200 $cm^{-1}$ (COOH); 1690 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.27 (s, 3, $ArCH_3$); δ1.83-2.80 (m, 6, $CH_2$); δ3.67 (s, 3, $ArOCH_3$); δ3.75 (s, 3, $ArOCH_3$); δ6.57 (s, 2, ArH); δ10.6 (s, 1, COOH).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.84; H, 7.75.

3,4-Dihydro-5,8-dimethoxy-6-methyl-1(2H)-naphthalenone 66. Hydrate. Following the method of Moore and Rahm (208), the acid 78 1.0 g (4.2 millimole) was stirred with 20 g of polyphosphoric acid and heated to 85° for 40 min. The red solution was poured onto 50 g of ice-water and stirred until all of the PPA solution had dissolved. The aqueous mixture was extracted with several portions of ether, the ether washed with water, 5% $NaHCO_3$ solution, washed again with water and the ether removed under reduced pressure. The residue was taken to dryness several times from benzene to remove traces of water, and was recrystallized from ether-hexane, mp 50-52°. Yield, 0.67 g (73%). ir (KBr) 3560 $cm^{-1}$ sharp (OH); 3500 $cm^{-1}$, shoulder, sharp (OH); 1650 $cm^{-1}$ (C=O); 1635 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.02 (s, ca. 3, HOH); δ2.07 (m, 2, $CH_2$); δ2.33 (s, 3, $CH_3$); δ2.60 (t, 2, $CH_2$); δ2.93 (t, 2, $CH_2$); δ3.70 (s, 3, $ArOCH_3$); δ3.88 (s, 3, $ArOCH_3$); δ6.69 (s, 1, ArH).

Anal. Calcd for $C_{13}H_{16}O_3 \cdot 1.2\ H_2O$: C, 64.50; H, 7.66. Found: C, 64.51; H, 7.52.

3,4-Dihydro-5,8-dimethoxy-6-methyl-1(2H)-naphthalenone 66. As described above, 5 g (22 millimole) of 78 was stirred with 100 g PPA for 35 min at 80°. The reaction was poured over 300 g ice-water and worked up as before. The residual oil obtained after removal of the solvent was not crystallized but was vacuum distilled, bp 149-150°/0.1 mm Hg, and the desired tetralone obtained as an extremely viscous pale yellow oil. Yield, 4.0 g (86.5%). ir (neat) 1675 $cm^{-1}$ (C=O); 1600 $cm^{-1}$ (C=C). nmr ($CDCl_3$) δ2.07 (m, 2, $CH_2$); δ2.33 (s, 3, $ArCH_3$); δ2.60 (t, 2, $CH_2$); δ2.93 (t, 2, $CH_2$); δ3.72 (s, 3, $ArOCH_3$); δ3.90 (s, 3, $ArOCH_3$); δ6.70 (s, 1, ArH).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.29. Found: C, 70.63; H, 7.50.

2-Bromo-3,4-dihydro-5,8-dimethoxy-6-methyl-1(2H)-naphthalenone 92. By a modification of the method of Wilds (217), 3.9 g (17.7 millimole) of the tetralone 66 was dissolved in 100 ml of dry ether and cooled to 5°. A solution of 2.84 g (17.8 millimole) of bromine in 10 ml of $CHCl_3$ was added dropwise over 0.5 hr. A yellow precipitate initially formed which dissolved on stirring a further 3 hr. The solution was washed with 2 x 100 ml of $H_2O$, 2 x 150 ml 2%

$NaHCO_3$, and then washed with water until the washings were neutral. The ether was dried ($Na_2SO_4$) and removed under reduced pressure. The residue was recrystallized from ethyl acetate-hexane, mp 77-78°. Yield, 4.3 g (81%). ir (KBr) 1670 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.35 (s, 3, $ArCH_3$); δ2.42 (m, 2, $CH_2$); δ3.13 (t, 2, $CH_2$); δ3.75 (s, 3, $ArOCH_3$); δ3.90 (s, 3, $ArOCH_3$); δ4.64 (t, 1, CH-Br); δ6.72 (s, 1, ArH).

Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 51.85; H, 5.09.

2-Nitro-3,4-dihydro-5,8-dimethoxy-6-methyl-1(2H)-naphthalenone 93. Following a modification of the method of Kornblum, et al,(212) 3.89 g (13 millimole) of the bromoketone 92 was added to a stirring solution of 1.79 g (26 millimole) of $NaNO_2$ and 2.27 g (14 millimole) of phloroglucinol in 12 ml of dry DMSO, and the mixture stirred for 2 hr. The solution was then poured into 250 ml of cold $H_2O$ and the precipitated solid collected by filtration and recrystallized from absolute ethanol (carbon), mp 141-142°. Yield, 2.2 g (63.7%). ir (KBr) 1675 $cm^{-1}$ (C=O); 1550 $cm^{-1}$ ($NO_2$). nmr ($CDCl_3$) δ2.35 (s, 3, $ArCH_3$); δ2.48-3.32 (m, 4, $CH_2$); δ3.72 (s, 3, $ArOCH_3$); δ3.88 (s, 3, $ArOCH_3$); δ5.36 (m, 1, $CH-NO_2$); δ6.74 (s, 1, ArH).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.04; H, 5.73; N, 4.95.

1-Hydroxy-2-amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene hydrochloride 94. The nitrotetralone 93, 1.51 g (5.7 millimole) was dissolved in 100 ml of dry benzene and added to a stirring solution of 13.15 g (45.6 millimole) (as a 70% solution) of bis-(2-methoxyethoxy)-aluminum hydride (Red-Al$^{R}$; Aldrich) in 50 ml of benzene. After addition, an additional 50 ml of benzene was added to the reaction. The solution was refluxed with stirring for 8 hr, then cooled and decomposed by addition of 100 ml of $H_2O$. The benzene layer was separated and the aqueous phase filtered to remove alumina salts and then extracted with 3 x 100 ml of $CHCl_3$. The chloroform and benzene solutions were combined, dried ($Na_2SO_4$), and the solvents removed under reduced pressure. The residue was taken up into ether-$CHCl_3$ (4:1) and dry HCl added to precipitate the salt. The crude salt as isolated was very hygroscopic and was dried in a vacuum dessicator. Yield, 0.97 g (62%). Mp (crude) 80-84°. ir (KBr) 3450 $cm^{-1}$ (OH); 2900 $cm^{-1}$ ($NH_3^+$). The salt was not further characterized and was used directly in the next step.

2-Amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene hydrochloride 44. By a modification of the method of Sprenger and Cannon (214) the crude amino alcohol 94, 950 mg (3.48 millimole), 19 ml of AcOH, 0.5 ml of 70% perchloric

acid, and 500 mg of 10% palladium-on-charcoal were placed in a 500 ml Parr bottle and shaken at an initial hydrogen pressure of 50 psig. Shaking was continued for 5 hr at room temp, at which time hydrogen uptake had ceased with about 75% of the theoretical amount of hydrogen absorbed. The catalyst was removed by filtration. To the filtrate was added 1.6 g of potassium acetate, the mixture stirred for 10 min, and then filtered to remove precipitated $KClO_4$. The filtrate was concentrated in vacuo and the residual oil taken up into 50 ml of $H_2O$ and basified with 10% NaOH solution. The basic solution was extracted with 3 x 50 ml of ether, the ether extracts combined and washed with water until the washings were neutral. The ether was removed under reduced pressure and the residual oil diluted with benzene and reduced in vacuo several times to remove traces of water. The residual brown oil was taken up into dry ether and the HCl salt precipitated with dry HCl gas and collected by filtration. The salt was twice recrystallized from isopropanol-ether (charcoal) to yield 388 mg (43.5%) of white crystals. Mp 237.5-238.5°. (Overall yield from nitrotetralone, 27%). ir (KBr) 2900 $cm^{-1}$ ($NH_3^+$). nmr (free base in $CHCl_3$) δ1.17-2.0 (m, 3, $-CH_2-$, -CH-); δ2.17 (s, 2, $NH_2$); δ2.33-3.17 (m, 4, $CH_2$); δ2.28 (s, 3, $ArCH_3$); δ3.72 (s, 3, $ArOCH_3$); δ3.80 (s, 3, $ArOCH_3$); δ6.55 (s, 1, ArH).

Anal. Calcd for $C_{13}H_{20}NO_2Cl$: C, 60.57; H, 7.82; N, 5.43. Found: C, 60.30; H, 7.83; N, 5.47.

## Part III.

Methylaminoacetone ethylene ketal 97. Prepared by the method of Kornfeld, et al,(216) from chloroacetone ethylene ketal and liquid methylamine. Yield, 79%, bp 72°/16 mm Hg, [lit (216) bp 160-162°]. ir (neat) 3315 $cm^{-1}$ (NH); 1220 $cm^{-1}$ (C-O str). nmr ($CDCl_3$) δ1.37 (s, 3, N-$CH_3$); δ1.42 (s, 1, NH); δ2.47 (s, 3, $CH_3$); δ2.70 (s, 2, -$CH_2$N-); δ3.98 (2, 4, -$OCH_2CH_2O$-).

α-[N-Methyl-N-(2-methyl-1,3-dioxolan-2-yl-methyl)amino]-acetophenone 98a. Similar to the method of Kornfeld, et al, (216) α-bromoacetophenone, 19.9 g (0.10 mole), and 40.61 g (0.31 mole) of 97 were refluxed together in 200 ml of dry benzene, under $N_2$, for 24 hr. The mixture was cooled and the HBr salt of the excess amine removed by filtration (21 g, 99% of the bromine). The benzene filtrate was reduced in vacuo. Excess aminoketal 97 was stripped off on the steam bath under house vacuum and the residual oil vacuum distilled, bp 143°/1.5 mm Hg. Yield, 20.8 g (83.5%). ir (neat) 1690 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ1.37 (s, 3, -$CH_3$);

δ2.52 (s, 3, N-$CH_3$); δ2.72 (s, 2, -$C\underline{H}_2$-N-); δ3.93 (s, 4, -$OCH_2CH_2O$-); δ4.02 (s, 2, $COC\underline{H}_2N$-); δ7.50 (m, 3, ArH); δ8.10 (m, 2, ArH).

Further characterized as the HCl salt, mp 148-151° (acetone). nmr (DMSO) δ1.47 (s, 3, $CH_3$); δ3.08 (s, 3, N-$CH_3$); δ3.57 (s, -$C\underline{H}_2N$-); δ4.02 (s, 4, -$OCH_2CH_2O$-); δ5.14 (s, 2, $COC\underline{H}_2N$-); δ7.74 (m, 3, ArH); δ7.81 (m, 2, ArH).

Anal. Calcd for $C_{14}H_{20}ClNO_3$: C, 58.83; H, 7.05; N, 4.90. Found: C, 58.54; H, 7.11; N, 5.25.

2,5-Dimethoxy-4-methylacetophenone 95b. 2,5-Dimethoxytoluene, 60.8 g (0.4 mole) and 31.4 g (0.4 mole) of acetyl chloride were dissolved in 400 ml of $CH_2Cl_2$ and cooled to 0°. Anhydrous $SnCl_4$, 104 g (0.44 mole), was added, dropwise, maintaining the temperature between 0-10°. After addition was complete the solution was allowed to warm to room temperature and stir 0.5 hr, and was heated to reflux for 2 hr. The mixture was stirred overnight at room temperature then poured over 100 g of ice. The aqueous layer was separated and discarded and the organic phase washed with 250 ml of 6N HCl and 2 x 200 ml of $H_2O$. The organic layer was dried ($Na_2SO_4$) and reduced in vacuo. The residual solid was recrystallized from MeOH-$H_2O$, yield 89%, mp 74-76°. [lit (203) mp 74°]. ir (KBr) 1660 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.27 (s, 3, $ArCH_3$); δ2.62 (s, 3, $COCH_3$); δ3.84 (s, 3, $ArOCH_3$); δ3.88 (s, 3, $ArOCH_3$); δ6.82 (s, 1, ArH); δ7.31 (s, 1, ArH).

2,5-Dimethoxy-4-methyl-α-bromoacetophenone 96b. Based on Wild's procedure (217), 48.5 g (0.25 mole) of 95b was dissolved in 700 ml dry ether and cooled to 5°. Bromine, 34.9 g (0.25 mole) was added dropwise over 1 hr. Toward the end of the addition the mixture became thick and an additional 250 ml of ether was added. The resulting thick slurry was allowed to warm to room temperature and stirred overnight. Sufficient ether was then added to dissolve all solid material (ca. 2 l) and the ether solution was washed with 3 x 750 ml of $H_2O$, 1 x 500 ml of 5% $Na_2CO_3$, and then washed with water until the washings were neutral. The ether was dried ($Na_2SO_4$) and removed under reduced pressure. The residual solid was crystallized from $CHCl_3$-hexane, mp 114.5-115.5°. Yield, 55.9 g (82%). ir (KBr) 1675 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ2.28 (s, 3, $ArCH_3$); δ3.85 (s, 3, $ArOCH_3$); δ3.93 (s, 3, $ArOCH_3$); δ4.64 (s, 2, $CH_2Br$); δ6.85 (s, 1, ArH); δ7.36 (s, 1, ArH).

Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 41.27; H, 4.09. Found: C, 41.02; H, 3.72.

α-[N-Methyl-N(2-methyl-1,3-dioxolan-2-yl-methyl)amino]-2,5-dimethoxy-4-methylacetophenone 98b. Similar to the preparation of 98a, 27.3 g (0.1 mole), of 96b and 40.61 g (0.31 mole) of 97 were refluxed together under $N_2$ overnight in 300 ml of dry benzene. The mixture was cooled, and filtered to remove the HBr salt of excess 97 (20.5 g, 97% of bromine

removed). The benzene filtrate was reduced *in vacuo* and the residual oil taken up in 10:1 pentane-benzene and cooled in a solid $CO_2$-acetone bath with vigorous scratching. The amorphous yellow solid was collected by filtration and washed on the filter with cold pentane. Yield, 27.6 g (85%). Pure material was recrystallized from hexane-benzene as waxy yellow needles, mp 69-71°. ir (KBr) 1670 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ1.37 (s, 3, $CH_3$); δ2.25 (s, 3, $ArCH_3$); δ2.57 (s, 3, $N-CH_3$); δ2.75 (s, 2, $CH_2-N$); δ3.83 (s, 3, $ArOCH_3$); δ3.87 (s, 3, $ArOCH_3$); δ3.95 (s, 4, $OCH_2-$); δ4.07 (s, 2, $COCH_2N-$); δ6.80 (s, 1, ArH); δ7.31 (s, 1, ArH).

The material was further characterized as its HCl salt, mp 132.5-133.5° (acetone). nmr (DMSO) δ1.45 (s, 3, $CH_3$); δ2.26 (s, 3, $ArCH_3$); δ3.05 (s, 3, $N-CH_3$); δ3.53 (s, 2, $CH_2-N$); δ3.82 (s, 3, $ArOCH_3$); δ3.95 (s, 3, $ArOCH_3$); δ4.02 (s, 4, $-OCH_2CH_2O-$); δ4.78 (s, 2, $COCH_2-N$); δ7.20 (s, 1, ArH); δ7.36 (s, 1, ArH).

Anal. Calcd for $C_{17}H_{26}ClNO_5$: C, 56.74; H, 7.28; N, 3.89. Found: C, 56.53; H, 7.31; N, 3.70.

2,5-Dimethoxy-4-bromotoluene 105. By a modification of the method of Harley-Mason (163), 45.4 g (0.298 mole) of 2,5-dimethoxytoluene (Eastman) was dissolved in 200 ml AcOH and cooled to 10°. A solution of 48 g (0.3 mole) of $Br_2$ in 150 ml of AcOH was added over 30 min, during which time an

orange precipitate formed. The mixture was stirred overnight at room temperature, then poured over 1,000 g ice-$H_2O$ and the precipitate collected by suction filtration. The solid material was reslurried in fresh $H_2O$, refiltered, and dried. Yield, 64 g (92.8%). Recrystallized from methanol, yield, 60.5 g (87.6%), mp 91.5-92° [lit (222) mp 91°]. nmr ($CDCl_3$) δ2.24 (s, 3, $ArCH_3$); δ3.81 (s, 6, $ArOCH_3$); δ6.68 (s, 1, ArH); δ6.92 (s, 1, ArH).

Ethyl sarcosinate 111. Sarcosine ethyl ester hydrochloride was prepared from sarcosine, ethanol, and dry HCl gas by a modification of the method of Werbin and Spoerri (244), yield, 68%, mp 120-122° [lit (245) mp 121-122°]. The free base was liberated from the HCl salt with cold KOH soln by the method of Leonard and Barthel (246). Yield, 49.5%, bp 50-55°/17 mm, [lit (237) bp 50-55°/17 mm].

Formyl succinate 110. Prepared from diethyl succinate and ethyl formate by the method of Wislicenus, et al (223), bp 72°/0.4 mm Hg, [lit (224) bp 137°/15 mm]. Yield, 77.5% of material slightly impure by tlc (silica-gel-ether), but which was used directly in the next step.

Ethyl-[N-methyl-N-(2,3-dicarbethoxy-1-propen-1-yl)amino]-acetate 112. Following a modification of the method of Plieninger (37) 98.5 g (0.488 mole) of formyl succinate 110

was dissolved in 200 ml of benzene, cooled to 10°, and 57 g (0.488 mole) of ethyl sarcosinate 111 added. The mixture was heated to reflux and water continuously removed as formed (Dean-Stark). Reaction was stopped when no more water was formed and the benzene was removed in vacuo. The residue was vacuum distilled, bp 147-149°/0.075 mm Hg. On standing the distillate solidified and was recrystallized from ether-hexane, mp 44.5-45.5°. Yield, 89%. ir (neat) 1730 $cm^{-1}$ (C=O); 1680 and 1690 $cm^{-1}$ (doublet) (C=O); 1625 $cm^{-1}$ (C=C). nmr ($CDCl_3$) δ1.25 (3t, 9, $CH_3$); δ3.10 (s, 3, N-$CH_3$); δ3.43 (s, 2, $CH_2$); δ3.97 (s, 2, CO$CH_2$-N); δ4.17 (3q, 6, O-$CH_2$-); δ7.45 (s, 1, =C<u>H</u>-N-).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.64. Found: C, 55.61; H, 7.90; N, 4.52.

Ethyl [N-methyl-N-(2,3-dicarbethoxypropyl)-amino]-acetate 113. Following a modification of the method of Borch, et al,(224) 30.1 g (0.1 mole) of the enamine 112 was dissolved in 200 ml of absolute ethanol. Sodium cyanoborohydride (Alfa Inorganics) 6.46 g (0.103 mole) was added all at once, and the pH monitored with pH paper and maintained at about 3-4 by addition of 2N ethanolic HCl. A total of 90 ml of the ethanolic HCl was added over about 30 min. After 1 hr reaction time, tlc analysis revealed that no starting material remained. The reaction mixture was concentrated in vacuo, the residue dissolved in 1,000 ml of

cold $H_2O$, made basic by addition of solid $K_2CO_3$, and the basic solution extracted with 4 x 400 ml of ether. The ether extracts were dried ($Na_2SO_4$) and the ether removed in vacuo. The residue was vacuum distilled, bp 128-130°/ 0.6 mm Hg. Yield, 29.1 g (96%). ir (neat) 1730 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ1.27 (t, 9, 3 x $OCH_2$-$CH_3$); δ2.42 (s, 3, N-$CH_3$); δ2.55-3.05 (m, 5, -CH-; -$CH_2$-); δ3.30 (s, 2, $COCH_2N$-); δ4.17 (3q, 6, O-$CH_2$-$CH_3$).

Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.50; H, 8.25; N, 4.62. Found: C, 55.57; H, 8.52; N, 4.40.

Dieckmann cyclization of triester 113. Following the procedure of Plieninger (37) 3.53 g (0.153 mole) of sodium was dissolved in 80 ml of absolute EtOH. Toluene, 200 ml, was added and the ethanol was removed by azeotropic distillation. Additional toluene was added to maintain the volume. A solution of 30.3 g (0.1 mole) of the aminotriester 113 in 60 ml of toluene was added slowly and the ethanol distilled out as formed as the azeotrope. The mixture was refluxed for 2 hr and cooled. Next, 40 ml of concentrated HCl was added and the mixture was refluxed with vigorous stirring for 48 hr, until an aliquot of the aqueous layer no longer gave a positive ferric chloride test. The reaction mixture was then cooled and concentrated under reduced pressure. The entire mixture was taken up in 200 ml of absolute EtOH and reduced in vacuo. This process was

repeated several times to remove all traces of water. Finally, 400 ml of absolute EtOH was added to the viscous brown residue and the solution saturated with dry HCl gas and allowed to stir at room temp for 48 hr. The ethanolic solution was then concentrated in vacuum, the residue taken up in cold $H_2O$, neutralized with solid $K_2CO_3$, and the liberated aminoesters extracted into ether. The ether solution was dried ($Na_2SO_4$) and concentrated in vacuo. The residual oil was vacuum distilled, bp 125-135°/10-12 mm Hg. Yield, 15.4 g. Tlc (silica gel-ether) showed three major components with $R_f$ = 0.55, 0.35, and 0.20, and one minor component at $R_f$ = 0.47.

Preparative column chromatographic isolation of Dieckmann products 108, 116, and 118. A 50 x 1,000 mm column was packed with 650 g of degassed silica gel (J. T. Baker, 60-200 mesh) in ether. Seventeen grams of the mixture of products obtained from a Dieckmann cyclization was applied to the column and eluted with ether. The effluent was monitored by tlc and eluted fractions of like composition were combined and the ether removed. A total of 13.95 g (82% recovery) was obtained from the column. Component "1" ($R_f$ = 0.55) was eluted first and 8.45 g obtained. The yields of components "3" ($R_f$ = 0.35) and component "4" ($R_f$ = 0.20) were 1.0 g and 4.55 g, respectively.

Identification of component "1," N-methyl-5-carbethoxy-3-piperidone diethylketal 116. Obtained from the column in 60.5% yield and purified by vacuum distillation, bp 140-142°/9-11 mm Hg. ir (neat) 1732 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ1.15 (t, 3, $-CH_2C\underline{H}_3$); δ1.20 (t, 3, $-CH_2C\underline{H}_3$); δ1.23 (t, 3, $-CH_2C\underline{H}_3$); δ1.61-3.20 (m, 7, -CH-, $-CH_2-$); δ2.33 (s, 3, $N-CH_3$); δ3.50 (q, 2, $O-C\underline{H}_2CH_3$); δ3.57 (q, 2, $O-C\underline{H}_2CH_3$); δ4.15 (q, 2, $O-C\underline{H}_2CH_3$). This compound was further characterized as the hydrochloride salt, mp 138-138.5° ($EtOH-Et_2O$).

Anal. Calcd for $C_{13}H_{26}ClNO_4$: C, 52.78; H, 8.86; N, 4.73. Found: C, 53.17; H, 9.03; N, 5.06.

Identification of component "3," proposed to be N-methyl-5-carbethoxy-3-piperidone 108. Obtained from the column in 7% yield. ir (neat) 1732 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ1.27 (t, 3, $-CH_2C\underline{H}_3$); δ2.36 (s, 3, $N-CH_3$); δ2.44-3.33 (m, 7, -CH-, $-C\underline{H}_2-$); δ4.20 (q, 2, $-O-C\underline{H}_2CH_3$). Further characterized as the hydrochloride salt and recrystallized from $EtOH-Et_2O$, mp 96-97° (dec).

Anal. Calcd for $C_9H_{16}ClNO_3$: C, 48.76; H, 7.27; N, 6.32. Found: C, 48.64; H, 1.83-8.3; N, 5.34. Mass spectrometry (70 eV) showed a molecular ion at m/e = 185, as predicted.

Identification of component "4," N-methyl-4-ethoxycarbonyl methyl-3-pyrrolidone 118. Yield recovered from column, 32.5%. ir (neat) 1732 $cm^{-1}$ and 1760 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ1.25 (t, 3, $-CH_2\underline{CH_3}$); δ2.23-3.15 (m, 5, -CH-, $-CH_2-$); δ3.24-3.52 (m, 2, $-CH_2-$); δ2.47 (s, 3, $N-CH_3$); δ4.15 (q, 2, $-O-\underline{CH_2}CH_3$).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; O, 25.91. Found: C, 58.41; H, 8.12; N, 7.17; O, 25.84. Mass spectrometry (70 eV) showed a molecular ion at m/e = 185, as predicted.

Hexyl N-methyl-3,3-diethoxypiperidine-5-carboxylate 117. To a solution of 8.4 g (3.24 millimole) of the ester ketal 116 in 50 ml of dry 1-hexanol was added 100 mg of sodium metal. The sodium slowly dissolved and the mixture was stirred at room temperature under house vacuum (ca 50-80 mm) for 48 hr. The hexanol was removed under reduced pressure and the residual oil vacuum distilled, bp 115-117°/0.15 mm Hg. Yield, 8.65 g (85%). ir (neat) 1725 $cm^{-1}$ (C=O). nmr ($CDCl_3$) δ0.88 (t, 3, $R-CH_2\underline{CH_3}$); δ1.03-1.67 (m, 14, $-CH_2-$, $O-CH_2\underline{CH_3}$); δ1.62-2.93 (m, 7, -CH-, $-CH_2-$); δ2.32 (s, 3, $N-CH_3$); δ3.50 (q, 2, $O-\underline{CH_2}CH_3$); δ3.55 (q, 2, $O-\underline{CH_2}CH_3$); δ4.07 (q, 2, $O-\underline{CH_2}CH_3$).

Anal. Calcd for $C_{17}H_{33}NO_4$: C, 64.72; H, 10.54; N, 4.44; O, 20.28. Found: C, 64.95; H, 10.41; N, 4.29; O, 20.46.

Acid hydrolysis of the ketal-ester 116. A solution of 1.4 g (5.4 millimole) of 116 was dissolved in 7.0 ml of 3 N HCl (21 milliequiv) and stirred at 50° C (oil bath) under $N_2$ for 2.5 hr, at which time tlc analysis (silica gel-ether) indicated complete reaction. The solution was neutralized with solid $Na_2CO_3$ and then extracted with 10 x 20 ml of $CHCl_3$. The chloroform solution was washed with $H_2O$ and dried ($Na_2SO_4$). After removal of the $CHCl_3$ 250 mg of a yellow oil remained which had chromatographic mobility, ir, and nmr properties identical to component "3" 108 described above. Yield (crude) 25%.

Acid hydrolysis of the ketal-hexylester 117. A solution of 3.15 g (10 millimole) of 117 in 14 ml of 3 N HCl was stirred under $N_2$ at 45-50° (oil bath) for 4.5 hr, at which time tlc (silica gel-ether) indicated disappearance of the starting material ($R_f$ = 0.71) and formation of a new spot at $R_f$ = 0.57. The mixture was cooled, neutralized with solid $K_2CO_3$ and repeatedly extracted with ether. The ether extracts were washed with $H_2O$ and dried ($Na_2SO_4$). After removal of the ether, 1.0 g of an oil remained which had an ir spectrum similar to that for 108. The odor of hexanol was very pronounced and nmr analysis showed the presence of hexanol to the extent of about 42% (by integration ratios of the methylenes adjacent to the ester and alcohol oxygens at

δ3.65 and δ4.14, respectively). The nmr spectrum ($CDCl_3$) was identical to that for 108 with the exception of the absorptions due to the hexanol, and to the change from ethyl ester to hexyl ester. The crude residue was taken up into ether and the hydrochloride salt precipitated by addition of dry HCl gas. The crude tan solid was collected and recrystallized from EtOH-$Et_2O$. Mp 91.5-93° (dec).

Anal. Calcd for $C_{13}H_{24}ClNO_3$: C, 53.14; H, 8.23; N, 4.76; O, 21.78; Cl, 12.06. Found: C, 52.13; H, 8.60; O, 21.75; Cl, 12.22.

N-Methyl-4-hexyloxycarbonylmethyl-3-pyrrolidone 122. The Dieckmann cyclization described above was carried out but using 0.2 mole of sodium hydride as the cyclizing agent. No ethanol was distilled out. The reaction mixture was then worked up exactly as described previously using 1-hexanol instead of ethanol to give exclusively 8.5 g (35.3%) of the pyrrolidone ester 122, which was purified by vacuum distillation, bp 118-120°/0.17 mm Hg. The ir was similar to that for 118 with two carbonyls at 1760 $cm^{-1}$ and 1738 $cm^{-1}$. The nmr was virtually identical except for changes resulting from the hexyl ester. nmr ($CDCl_3$) δ0.88 (t, 3, R-$CH_2\underline{CH_3}$); δ1.33 (m, 8, -$CH_2$); δ2.47 (s, 3, N-$CH_3$); δ2.27-2.95 (m, 5, -CH-, -$CH_2$-); δ3.23-3.52 (m, 2, -$CH_2$-); δ4.10 (t, 2, O-$\underline{CH_2}$-$CH_2$-).

Cis-, and trans-N-methyl-4-(2-hydroxyethyl)-3-pyrrolidinol 121. To a stirring suspension of 558 mg (0.02 mole) of LAH in 50 ml of dry ether was added 2.41 g (0.01 mole) of 122. The mixture was refluxed with stirring for 4 hr and then cooled and carefully decomposed with 5 ml of $H_2O$. The alumina was removed by filtration and then extracted with $CHCl_3$. The $CHCl_3$ was combined with the ether filtrate and the organic solution dried ($Na_2SO_4$) and reduced in vacuo. The residue was vacuum distilled, bp 109-110°/0.1 mm Hg. Yield, 700 mg (53.4%). ir (neat) 3300 $cm^{-1}$ (OH). nmr ($CDCl_3$) δ1.5-3.17 (m, 7, -CH-, $-CH_2-$); δ2.32 (2s, 3, $N-CH_3$ cis and trans); δ3.53 (t, 2, $-CH_2CH_2OH$); δ3.88-3.97 (m, 1, CH-OH); δ4.35 (s, 2, OH).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.25; H, 10.03; N, 9.69.

# SUMMARY

Among considerations which have appeared in the literature regarding essential structural element(s) in lysergic acid alkaloids, one of the most interesting, and one which has received little recent attention, is the phenethylamine moiety. A comprehensive review of the pertinent literature showed that this element may be a primary factor in the activity of LSD-25. An aminotetralin fragment has also been proposed to be the essential element in lysergic acid, but in the view presented here this structure may be considered to be a rigid phenethylamine.

Synthesis and testing of selected bromomethoxyamphetamines gives support to the concept of relative importance of the para substituent for metabolic stability. Electronic or molecular orbital energy values did not correlate with activity for bromomethoxyamphetamines. Importance of the stereochemistry of the psychotomimetic amphetamines was emphasized, and a facile synthesis of the (+) and (-) enantiomers of amphetamines was developed. A rigid analog of DOM was prepared to examine the conformational requirements of the receptor involved in psychotomimetic activity.

Attempts were made to prepare an LSD AD-ring system, but an unexpected cyclization product was formed. The products of reaction were identified and explanations were offered for the results.

# BIBLIOGRAPHY


1. J. Delay, in "Neuro-Psychopharmacology," P. B. Bradley, P. Deniker, and C. Radouco-Thomas, Eds., Elsevier, Amsterdam, 1959, p. 167.

2. H. Osmond, Ann. N. Y. Acad. Sci., 66, 418 (1957).

3. A. Hofmann, Svensk. Kem. Tidskr., 72, 723 (1960).

4. D. F. Downing, Quart. Rev. (London), 16, 133 (1962).

5. K. A. Nieforth, J. Pharm. Sci., 60, 655 (1971).

6. "Psychotomimetic Drugs," D. Efron, Ed., Raven Press, 1970.

7. M. A. Davis, in "Annual Reports in Medicinal Chemistry," C. K. Cain, Ed., Academic Press, 1968, pp. 13-27.

8. S. Cohen, in "Progress in Drug Research," Vol. 15, Birkhauser Verlag, Basel, 1971, pp. 68-102.

9. P. Brawley and J. C. Duffield, Pharmacol. Rev., 24, 31-66 (1972).

10. A. Hofmann, in "Drugs Affecting the Central Nervous System," A. Burger, Ed., Arnold, London, 1968, pp. 169-226.

11. A. Hoffer and H. Osmond, "The Hallucinogens," Academic Press, New York, 1967.

12. A. Irvin, J. Psychedelic Drugs, 3, 5 (1971).

13. S. Cohen, Ann. Rev. Pharmacol., 7, 301 (1967).

14. L. Lewin, Arch. Exp. Pathol. Pharmakol., 24, 401 (1888); ibid., 34, 374 (1894).

15. A. Heffter, Chem. Ber., 29, 216 (1896).

16. E. Späth, Monatsh. Chem., 40, 129 (1919).

17. A. Hofmann, Acta Physiol. Pharmacol. (Neerl.), 8, 240 (1959).

18. H. Isbell, A. B. Wolbach, A. Wikler, and E. J. Miner, Psychopharmacologia, 2, 147 (1961).

19. G. Karreman, I. Isenberg, and A. Szent-Györgyi, Science, 130, 1191 (1959).

20. S. H. Snyder and C. R. Merril, Proc. Nat. Acad. Sci. U. S., 54, 258 (1965).

21. S. Kang and J. P. Green, ibid., 67, 62 (1970).

22. W. R. Martin and C. G. Eades, Psychopharmacologia, 17, 242 (1970).

23. J. K. Meek and K. Fuxe, Biochem. Pharmacol., 20, 693 (1971).

24. H. VanVunakis, J. T. Farrow, H. B. Gjika, and L. Levine, Proc. Nat. Acad. Sci. U. S., 68, 1483 (1971).

25. S. H. Snyder and E. Richelson, ibid., 60, 206 (1968).

26. S. H. Snyder and E. Richelson, in "Psychotomimetic Drugs," D. Efron, Ed., Raven Press, New York, 1970, p. 59.

27. C. Chothia and P. Pauling, Proc. Nat. Acad. Sci. U. S., 63, 1063 (1969).

28. P. D. Cooper and C. G. Walters, Nature, 238, 96 (1972).

29. A. Stoll and A. Hofmann, Helv. Chim. Acta, 38, 421 (1955).

30. A. T. Shulgin, T. Sargent, and C. Naranjo, Nature, 221, 537 (1969).

31. F. G. H. Lee, J. W. Daly, and A. A. Manian, J. Med. Chem., 12, 321 (1969).

32. J. R. Smythies, J. Beaton, F. Benington, and R. D. Morin, Nature, 226, 644 (1970).

33. B. E. Leonard and P. D. Stonier, Psychopharmacologia, 25, 1 (1972).

34. H. C. Cheng, D. E. Nichols, J. P. Long, and C. F. Barfknecht, unpublished results.

35. E. Campaigne and D. R. Knapp, J. Pharm. Sci., 60, 809 (1971).

36. S. E. Jordan, A. Lasslo, H. L. Livingston, H. Alpern, and A. Gersing, Arch. Int. Pharmacodyn. Ther., 115, 452 (1958).

37. H. Plieninger, Chem. Ber., 86, 25 (1953).

38. J. Sivadjian, C. R. Acad. Sci., Paris, Ser. C, 270, 2499 (1970).

39. S. N. Pradhan and S. N. Dutta, Psychopharmacologia, 17, 49 (1970).

40. N. J. Mattila, L. Ahtee, and L. Saarnivaara, Ann. Med. Exp. Biol. Fenniae (Helsinki), 46, 78 (1968).

41. A. S. V. Burgen, J. Pharm. Pharmacol., 16, 638 (1964).

42. A. Herz, Naunyn-Schmiedebergs Arch. Exp. Path. u. Pharmak., 242, 414 (1962).

43. A. Herz and F. Yacoub, Psychopharmacologia, 5, 115 (1964).

44. C. C. Pfeiffer and E. H. Jenney, Ann. N. Y. Acad. Sci., 66, 753 (1957).

45. R. T. Coutts and J. R. Scott, Can. J. Pharm. Sci., 6, 78 (1971).

46. R. H. S. Thompson, A. Tickner, and G. R. Webster, Biochem. J., 58, XIX-XX (1954).

47. E. K. Zsigmont, V. M. Foldes, and F. F. Foldes, Psychopharmacologia, 4, 232 (1963).

48. J. Lehrfield, PhD Thesis, Univ. of Illinois, Chicago, Ill., 1966; Chem. Abstr., 65, 3829 (1966).

49. K. Hohenlohe-Ochringen, D. Saffer, G. Sporidi, and H. Bretschneider, Monatsh. Chem., 92, 313 (1961).

50. M. Julia, J. Igolen, and A. Kolb, C. R. Acad. Sci., Paris, Ser. C, 273, 1776 (1971).

51. G. Thuiller, B. Marcot, A. Vilar, and P. Rumpf, Bull. Soc. Chim. Fr., 1763 (1966).

52. J. R. Smythies, J. M. Beaton, F. Benington, and R. D. Morin, Eur. J. Pharmacol., 17, 270 (1972).

53. S. Sklar, K. A. Nieforth, and M. Malone, J. Pharm. Sci., 60, 304 (1971).

54. P. E. Norris and F. F. Blicke, J. Amer. Pharm. Ass. (Scientific ed.), XLI, 637 (1952).

55. J. H. Gaddum and N. J. Giarman, Brit. J. Pharmacol., 11, 88 (1956).

56. J. H. Gaddum, J. Physiol. (London), 121, 15P (1953).

57. D. W. Woolley and E. A. Shaw, Proc. Nat. Acad. Sci. U. S., 40, 228 (1954).

58. D. R. Curtis and R. Davis, Brit. J. Pharmacol., 18, 217 (1962).

59. A. Cerletti and E. Rothlin, Nature, 176, 785 (1955).

60. D. X. Freedman, R. Gottlieb, and R. A. Lovell, Biochem. Pharmacol., 19, 1181 (1970).

61. G. K. Aghajanian, J. A. Rosecrans, and M. H. Sheard, Science, 156, 402 (1967).

62. M. H. Sheard and G. K. Aghajanian, J. Pharmacol. Exp. Ther., 163, 425 (1968).

63. G. K. Aghajanian, W. E. Foote, and M. H. Sheard, Science, 161, 706 (1968).

64. D. X. Freedman and N. J. Giarman, Ann. N. Y. Acad. Sci., 96, 98 (1962).

65. S. M. Schanberg and N. J. Giarman, Biochem. Pharmacol., 11, 187 (1962).

66. A. Cerletti, in "Neuro-Pharmacology," P. B. Bradley, P. Deniker, and C. Radouco-Thomas, Eds., Elsevier, Amsterdam, 1959, p. 117.

67. G. K. Aghajanian, Ann. Rev. Pharmacol., 12, 157 (1972).

68. A. Burger, in "Medicinal Chemistry," Vol. II, A. Burger, Ed., John Wiley and Sons, New York, 1970, p. 1511.

69. C. W. Gorodetzky and H. Isbell, Psychopharmacologia, 6, 229 (1964).

70. G. B. Marini-Bettolo, S. Chiavarelli, and D. Bovet, Gazz. Chim. Ital., 80, 281 (1950); Chem. Abstr., 45, 3828 (1951).

71. S. Chiavarelli and G. B. Marini-Bettolo, ibid., 81, 89 (1951); Chem. Abstr., 45, 8990 (1951).

72. G. B. Marini-Bettolo and S. Chiavarelli, ibid., 81, 98 (1951); Chem. Abstr., 45, 8991 (1951).

73. G. B. Marini-Bettolo, S. Chiavarelli, and F. Bovet-Nitti, ibid., 81, 587 (1951); Chem. Abstr., 46, 5602 (1952).

74. S. Chiavarelli and G. B. Marini-Bettolo, ibid., 82, 86 (1952); Rend. 1st Super. Sanita, 15, 813 (1952); Chem. Abstr., 47, 6944 (1953).

75. G. B. Marini-Bettolo and M. R. Falco, Rend. 1st Super. Sanita, 15, 826 (1952); Chem. Abstr., 48, 4487 (1954).

76. G. B. Marini-Bettolo and S. Chiavarelli, ibid., 15, 837 (1952); Chem. Abstr., 48, 4488 (1954).

77. G. B. Marini-Bettolo, R. L. Vittory, and D. Bovet, ibid., 15, 844 (1952); Chem. Abstr., 48, 4488 (1954).

78. G. B. Marini-Bettolo, H. A. Frediani, and S. Chiavarelli, ibid., 15, 850 (1952); Chem. Abstr., 48, 4489 (1954).

79. S. Chiavarelli, R. L. Vittory, M. Marzadro, and G. Palazzo, ibid., 15, 862 (1952); Chem. Abstr., 48, 4489 (1954).

80. D. Bovet, F. Bovet-Nitti, L. Sollero, and G. B. Marini-Bettolo, Experientia, 7, 232 (1951).

81. A. Kraushaar, Arzneim.-Forsch., 4, 273 (1954).

82. E. Rothlin, Arch. f. Exp. Path. u. Pharmakol., 181, 154 (1936).

83. J. N. Pennefather and R. H. Thorp, J. Pharm. Pharmacol., 10, 249 (1958).

84. R. Violland, N. Violland-Duperret, H. Pacheco, G. Trouiller, and A. LeBlanc, Bull. Chim. Ther., 196 (1971).

85. R. Violland, N. Violland-Duperret, and H. Pacheco, Bull. Soc. Chim. Fr., 307 (1971).

86. C. F. Barfknecht, D. E. Nichols, B. Olesen, and J. A. Engelbrecht, Pharmacologist, 13, 233 (1971).

87. C. F. Barfknecht, D. E. Nichols, D. B. Rusterholz, J. P. Long, J. A. Engelbrecht, J. M. Beaton, R. J. Bradley, and D. C. Dyer, Submitted for publication in J. Med. Chem.

88. J. P. Green, K. Dressler, and N. Khazan, "Mescaline-like Activity of 2-Amino-7-hydroxytetralin: A Prediction of Quantum Mechanics," manuscript in preparation.

89. W. Voigtlander, Pharmazie, 14, 318 (1959).

90. Z. Horii, T. Watanabe, T. Kurihara, and Y. Tamure, Chem. Pharm. Bull. (Tokyo), 13, 420 (1965).

91. B. B. Brodie, S. Spector, and P. A. Shore, Pharmacol. Rev., 11, 548 (1959).

92. E. Costa, G. L. Gessa, C. Hirsch, R. Kuntzman, and B. B. Brodie, Ann. N. Y. Acad. Sci., 96, 118 (1962).

93. E. Clemente and V. P. Lynch, J. Pharm. Sci., 57, 72 (1968).

94. N. Matussek and A. Halbach, Psychopharmacologia, 5, 158 (1964).

95. A. K. Dixon, Experientia, 15, 743 (1968).

96. O. Resnick, D. M. Krus, and M. Radkin, Life Sci. (Oxford), 4, 1433 (1965).

97. M. Goldstein, Pharmacol. Rev., 18, 77 (1966).

98. G. N. Woodruff, R. J. Walker, and G. A. Kerkut, Eur. J. Pharmacol., 14, 77 (1971).

99. G. N. Woodruff and R. J. Walker, Int. J. Neuropharmacol., 8, 279 (1969).

100. H. Nyback, Z. Borzecki, and G. Sedvall, Eur. J. Pharmacol., 4, 395 (1968).

101. R. Laverty and D. F. Sharman, Brit. J. Pharmacol., 24, 759 (1965).

102. R. E. Dill, Arch. Int. Pharmacodyn. Ther., 195, 320 (1972).

103. S. H Snyder, Arch. Gen. Psychiat., 27, 169 (1972).

104. P. H. Connell, "Amphetamine Psychosis," Maudsley Monographs, No. 5, Oxford Univ. Press, London, 1958.

105. A. Faurbye, Comp. Psychiat., 9, 155 (1968).

106. B. Angrist and S. Gershon, Pharmakopsychiat. Neuro-Psychopharmakol., 4, 64 (1971).

107. B. M. Angrist, B. Shopsin, and S. Gershon, Nature, 234, 152 (1971).

108. K. M. Taylor and S. H. Snyder, Science, 168, 1487 (1970).

109. S. H. Snyder, K. M. Taylor, J. R. Coyle, and J. L. Meyerhoff, Amer. J. Psychiat., 127, 199 (1970).

110. K. M. Taylor and S. H. Snyder, Brain Res., 28, 295 (1971).

111. L. C. F. Hanson, Psychopharmacologia, 10, 289 (1967).

112. R. B. Jenkins and R. H. Groh, Lancet, ii, 177 (1970).

113. R. Baltzly, V. Dvorkovitz, and A. P. Phillips, J. Amer. Chem. Soc., 71, 1162 (1949).

114. R. Baltzly and A. P. Phillips, ibid., 71, 3419 (1949).

115. H. G. Leeman and S. Fabbri, Helv. Chim. Acta, 42, 2696 (1959).

116. P. Stadler and A. Hofmann, ibid., 45, 2005 (1962).

117. H. B. Murphee, E. H. Jenney, and C. C. Pfeiffer, Pharmacologist, 2, 64 (1960).

118. C. F. Barfknecht and D. E. Nichols, J. Med. Chem., 15, 109 (1972).

119. A. T. Shulgin, J. Pharm. Pharmacol., in press.

120. F. Benington, R. D. Morin, J. R. Smythies, J. M. Beaton, and R. J. Bradley, unpublished results.

121. C. F. Barfknecht and D. E. Nichols, J. Med. Chem., 14, 370 (1971).

122. A. T. Shulgin, T. Sargent, and C. Naranjo, Pharmacology, 5, 103 (1971).

123. J. T. Coyle and S. H. Snyder, J. Pharmacol. Exp. Ther., 170, 221 (1969).

124. S. H. Snyder, M. J. Kuhar, A. I. Green, J. T. Coyle, and E. G. Shasken, in "International Review of Neurobiology," Vol. 1e, C. C. Pfeiffer and J. R. Smythies, Eds., Academic Press, New York, 1970, pp. 127-158.

125. D. Morgan, S. Lofstrandh, and E. Costa, Life Sci. (Oxford), 11, pt. 1, 83 (1972).

126. E. D. Hendley and S. H. Snyder, Eur. J. Pharmacol., 19, 56 (1972).

127. A. H. Beckett and S. Al-Sarraj, J. Pharm. Pharmacol., 24, 174 (1972).

128. C. C. Pfeiffer, Science, 124, 29 (1956).

129. E. Gordis, Biochem. Pharmacol., 15, 2124 (1966).

130. A. W. Schrecker and J. L. Hartwell, J. Amer. Chem. Soc., 79, 3827 (1957).

131. F. Zymalkowski and E. Dornhege, Justus Liebigs Ann. Chem., 728, 144 (1969).

132. B. Costall and R. J. Naylor, Life Sci. (Oxford), 11, pt. 1, 239 (1972).

133. M. B. Bowers, Jr., and R. H. Roth, Brit. J. Pharmacol., 44, 301 (1972).

134. R. O'Keefe, D. F. Sharman, and M. Vogt, ibid., 38, 287 (1970).

135. J. T. Coyle and S. H. Snyder, Science, 166, 899 (1969).

136. D. R. Haubrich and W. D. Reid, J. Pharmacol. Exp. Ther., 181, 19 (1972).

137. P. K. Gessner and I. H. Page, Amer. J. Physiol., 203, 167 (1961).

138. E. D. Hendley and S. H. Snyder, Nature, 229, 264 (1971).

139. S. H. Snyder, L. Faillace, and L. Hollister, Science, 158, 669 (1967).

140. C. Mitoma, Proc. Soc. Exp. Biol. Med., 134, 1162 (1970).

141. A. T. Shulgin, Experientia, 20, 366 (1964).

142. T. W. Sargent, D. M. Israelstam, A. T. Shulgin, S. A. Landlaw, and N. N. Finley, Biochem. Biophys. Res. Commun., 29, 126 (1967).

143. J. W. Schweitzer and A. J. Friedhoff, Biochem. Pharmacol., 15, 2097 (1966).

144. C. R. Creveling, N. Dalgard, H. Shimizu, and J. W. Daly, Mol. Pharmacol., 6, 691 (1970).

145. J. M. Musacchio and M. Goldstein, Biochem. Pharmacol., 16, 693 (1967).

146. S. Kang and J. P. Green, Nature, 226, 645 (1970).

147. F. Antun, J. R. Smythies, F. Benington, R. D. Morin, C. F. Barfknecht, and D. E. Nichols, Experientia, 27, 62 (1971).

148. K. Bailey and D. Verner, J. Pharm. Sci., 61, 480 (1972).

149. Ming-Ta Sung and J. A. Parker, Proc. Nat. Acad. Sci. U. S., 69, 1346 (1972).

150. R. Foster and C. A. Fyfe, Trans. Faraday Soc., 61, 1626 (1965).

151. J. R. Smythies, V. S. Johnson, R. J. Bradley, F. Benington, R. D. Morin, and L. C. Clark, Nature, 216, 128 (1967).

152. J. M. Beaton, J. R. Smythies, F. Benington, R. D. Morin, and L. C. Clark, Nature, 220, 800 (1968).

153. S. H. Snyder, L. A. Faillace, and H. Weingartner, Amer. J. Psychiat., 125, 357 (1968).

154. S. H. Snyder, L. A. Faillace, and H. Weingartner, Arch. Gen. Psychiat., 21, 95 (1969).

155. J. Knoll, in "Amphetamines and Related Compounds," E. Costa and S. Garattini, Eds., Raven Press, New York, 1970, p. 761.

156. B. T. Ho and L. W. Tansey, J. Med. Chem., 14, 156 (1971).

157. Linus Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell Univ. Press, Ithaca, New York, 1960, pp. 260-261.

158. S. Sepúlveda, R. Valenzuela, and B. K. Cassels, J. Med. Chem., 15, 413 (1972).

159. C. L. Johnson and J. P. Green, Beth Israel Medical Center, personal communication, 1972.

160. J. R. Smythies, E. A. Sykes, and C. P. Lord, Psychopharmacologia, 9, 434 (1966).

161. M. Tomita, T. Kikuchi, K. Bessho, and Y. Inubushi, Chem. Pharm. Bull. (Tokyo), 11, 1477 (1963).

162. J. S. Buck, R. Baltzly, and A. E. Ardis, J. Amer. Chem. Soc., 66, 311 (1944).

163. J. Harley-Mason, J. Chem. Soc., 200 (1953).

164. Z. Horii and T. Inoi, Yakugaku Zasshi, 77, 1095 (1957); Chem. Abstr., 52, 5319 (1958).

165. O. N. Tolkachev, V. P. Chernova, E. V. Kuznetsova, Fang-Lin Pao, and N. A. Preobrazhenskii, Zh. Obshch. Khim., 34, 545 (1964); Chem. Abstr., 60, 11925d (1964).

166. O. N. Tolkachev, V. P. Chernova, E. V. Kuznetsova, Fang-Lin Pao, and N. A. Preobrazhenskii, Zh. Org. Khim., 1, 719 (1965); Chem. Abstr., 63, 5546h (1965).

167. M. Tomita, K. Fujitani, and Y. Aoyagi, Tetrahedron Lett., 1201 (1967).

168. M. Tomita and H. Watanabe, J. Pharm. Soc. Japan, 58, 783 (1938); Chem. Abstr., 33, 2525 (1939).

169. K. Bessho, Chem. Pharm. Bull. (Tokyo), 11, 1491 (1963).

170. C. Viel, Ann. Chim. (Paris), 8, 515 (1963).

171. R. F. Nystrom and W. G. Brown, J. Amer. Chem. Soc., 70, 3738 (1948).

172. F. A. Ramirez and A. Burger, ibid., 72, 2781 (1950).

173. K. E. Hamlin and A. W. Weston, ibid., 71, 2210 (1949).

174. N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, 1956, p. 764.

175. G. Stork and H. Conroy, J. Amer. Chem. Soc., 73, 4743 (1951).

176. M. Erne and F. Ramirez, Helv. Chim. Acta, 33, 912 (1950).

177. G. W. Gray, B. Jones, and F. Marson, J. Chem. Soc., 1417 (1956).

178. K. C. Pandya, R. B. K. Pandya, and R. N. Singh, J. Indian Chem. Soc., 29, 363 (1952).

179. H. H. Hodgson and H. G. Beard, J. Chem. Soc., 127, 875 (1925).

180. B. T. Ho, W. M. McIsaac, R. An, L. W. Tansey, K. E. Walker, L. F. Englert, Jr., and M. B. Noel, J. Med. Chem., 13, 26 (1970).

181. C. B. Gairaud and G. R. Lappin, J. Org. Chem., 18, 1 (1953).

182. T. I. Crowell and C. E. Bell, ibid., 24, 1159 (1959).

183. J. R. Smythies, R. J. Bradley, V. S. Johnston, F. Benington, R. D. Morin, and L. C. Clark, Jr., Psychopharmacologia, 10, 379 (1967); C. F. Barfknecht, J. M. Miles, and J. L. Leseney, J. Pharm. Sci., 59, 1842 (1970).

184. N. Castagnoli, personal communication; R. A. Partyka, Bristol Laboratories, personal communication.

185. F. Weinges and G. Graab, Chem.-Ztg., Chem. App., 94, 728 (1970).

186. C. F. Barfknecht and D. E. Nichols, "Asymmetric Synthesis of Psychotomimetic Phenylisopropylamines," presented at the Division of Medicinal Chemistry, 164th National meeting of the American Chemical Society, New York, Aug., 1972, MEDI-006.

187. D. E. Nichols, C. F. Barfknecht, D. B. Rusterholz, F. Benington, and R. D. Morin, J. Med. Chem., in press.

188. J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).

189. J. W. Westley, B. Halpern, and B. L. Karger, Anal. Chem., 10, 2046 (1968).

190. C. E. Wells, J. Off. Ass. Anal. Chem., 55, 146 (1972).

191. D. Libermann, J. Himbert, L. Hengl, and G. Kirchhoffer, C. R. Acad. Sci. (Paris), Ser. C, 229, 265 (1949).

192. G. L. Lestina and H. W. J. Cressman, J. Org. Chem., 25, 1453 (1960).

193. R. C. Fuson and C. H. McKeever, in "Organic Reactions," Vol. 1, John Wiley and Sons, New York, N. Y., 1942, p. 63.

194. H. S. Corey, J. Amer. Chem. Soc., 86, 1884 (1964).

195. N. F. Elmore and T. J. King, J. Chem. Soc., 4425 (1961).

196. R. W. Krunnfusz, PhD Thesis, University of Iowa, 1972.

197. A. A. R. Sayigh, H. Ulrich, and M. Green, J. Chem. Soc., 3482 (1964).

198. J. Green, D. McHale, P. Mamalis, and S. Marcinkiewicz, ibid., 3374 (1959).

199. H. Gilman and C. F. Arntzen, J. Amer. Chem. Soc., 69, 1537 (1947).

200. A. Rieche, H. Gross, and E. Höft, Org. Syn., 47, 1 (1967).

201. C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Milwaukee, Wis., 1970, p. 681A.

202. L. Gattermann, Chem. Ber., 31, 1149 (1898).

203. R. Royer, P. Demerseman, A. Cheutin, E. Allegrini, and R. Michelet, Bull. Soc. Chim. Fr., 1379 (1957).

204. W. J. Moran, E. C. Schreiber, E. Engel, D. C. Behn, and J. L. Yamins, J. Amer. Chem. Soc., 74, 127 (1952).

205. R. Gritter, G. D. Dupre, and T. J. Wallace, Nature, 202, 179 (1964).

206. G. Jones, in "Organic Reactions," Vol. 15, John Wiley and Sons, New York, N. Y., 1967, p. 204.

207. M. S. Newman and P. F. Beal, III., J. Amer. Chem. Soc., 72, 5163 (1950).

208. J. A. Moore and M. Rahm, J. Org. Chem., 26, 1109 (1961).

209. W. K. Sprenger, PhD Thesis, University of Iowa, 1966.

210. J. C. Kim, PhD Thesis, University of Iowa, 1972.

211. R. I. Thrift, J. Chem. Soc., 288 (1967).

212. N. Kornblum, R. K. Blackwood, and J. W. Powers, J. Amer. Chem. Soc., 79, 2507 (1957).

213. D. Rusterholz, Univ. of Iowa, personal communication.

214. W. K. Sprenger, J. G. Cannon, B. K. Barman, and A. M. Burkman, J. Med. Chem., 12, 487 (1969).

215. H. A. Smith and R. G. Thompson, Advan. Catal., 9, 727 (1957).

216. E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, J. Amer. Chem. Soc., 78, 3087 (1956).

217. A. L. Wilds, J. Amer. Chem. Soc., 64, 1421 (1942).

218. J. Cymerman Craig, D. M. Temple, and B. Moore, Aust. J. Chem., 14, 84 (1961).

219. S. Shibata, M. Nakahara, and N. Aimi, Chem. Pharm. Bull. (Tokyo), 11, 379 (1963).

220. I. I. Lapkin and A. I. Golovkova, J. Gen. Chem. (USSR), 18, 485 (1948); Chem. Abstr., 42, 7273 (1948).

221. V. N. Gupta and T. R. Seshadri, Proc. Indian Acad. Sci., 44A, 223 (1956).

222. D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz, J. Chem. Soc., 1600 (1958).

223. W. Wislicenus, E. Boklen, and F. Reuthe, Justus Liebigs Ann. Chem., 363, 347 (1908).

224. R. F. Borch, M. D. Bernstein, and H. Dupont Durst, J. Amer. Chem. Soc., 93, 2897 (1971).

225. H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

226. C. D. Gutsche, "The Chemistry of Carbonyl Compounds," Prentice-Hall, New Jersey, 1967, pp. 47-48.

227. W. A. M. Davies, J. B. Jones, and A. R. Pinder, J. Chem. Soc., 3504 (1960).

228. E. Jaeger and J. H. Biel, J. Org. Chem., 30, 740 (1965).

229. Sadtler Nuclear Magnetic Resonance Spectra, Sadtler Research Laboratories, Philadelphia, Pa.

230. W. B. Thomas and S. M. McElvain, J. Amer. Chem. Soc., 56, 1806 (1934).

231. S. M. McElvain and P. M. Laughton, ibid., 73, 448 (1957).

232. M. E. Dobson, J. Ferns, and W. H. Perkin, Jr., J. Chem. Soc., 2010 (1909).

233. J. P. Schaefer and J. J. Bloomfield, in "Organic Reactions," Vol. 15, John Wiley and Sons, New York, N. Y., 1967, pp. 19-21.

234. M. J. D'Errico, PhD Thesis, Columbia University, 1960. Dissertation Abstr., 21, 52 (1960).

235. J. Dutta and R. N. Biswas, J. Indian Chem. Soc., 38, 335 (1961).

236. J. Dutta and R. N. Biswas, ibid., 38, 385 (1961).

237. D. K. Banerjee, J. Dutta, and G. Bagavant, Proc. Indian Acad. Sci., 46A, 80 (1957); Chem. Abstr., 52, 3701b (1958).

238. P. H. Beyer, Rec. Trav. Chim. Pays-Bas, 40, 621 (1921).

239. A. Rilliet, Helv. Chim. Acta, 5,550 (1922).

240. H. Erdtman and B. Leopold, Acta Chem. Scand., 2, 34 (1948).

241. A. Luttringhaus and H. Gralheer, Justus Liebigs Ann. Chem., 550, 67 (1941).

242. Y. Misaka, T. Mizutani, M. Sekido, and S. Uyeo, J. Chem. Soc., 2954 (1968).

243. W. Leithe, Chem. Ber., 65, 664 (1932).

244. H. Werbin and P. E. Spoerri, J. Amer. Chem. Soc., 69, 1681 (1947).

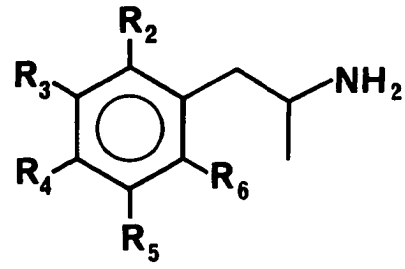
245. W. Staudt, Z. Physiol. Chem., 146, 286 (1925).

246. N. J. Leonard and E. Barthel, J. Amer. Chem. Soc., 72, 3632 (1950).

# APPENDIX A

## CALCULATED VALUES FOR THE ENERGY OF THE HIGHEST OCCUPIED MOLECULAR ORBITAL FOR CERTAIN CHLOROMETHOXYAMPHETAMINES

TABLE 1. VALUES FOR ENERGY OF THE HIGHEST OCCUPIED MOLECULAR ORBITAL FOR CERTAIN CHLOROMETHOXYAMPHETAMINES



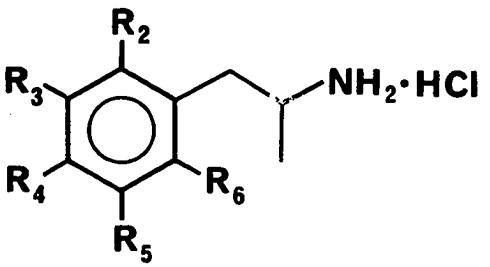

| Corresponds to Bromomethoxy Compound No. | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | HOMO ( units) |
|---|---|---|---|---|---|---|
| 43a | Cl | H | H | $OCH_3$ | H | -.5545 |
| 43b | H | Cl | $OCH_3$ | H | H | -.5469 |
| 43c | H | $OCH_3$ | Cl | H | H | -.5470* |
| 43d | Cl | H | $OCH_3$ | $OCH_3$ | H | -.5320 |
| 43e | H | $OCH_3$ | Cl | $OCH_3$ | H | -.5288* |
| 43f | $OCH_3$ | H | Cl | $OCH_3$ | H | -.5404* |
| --- | $OCH_3$ | H | $OCH_3$ | Cl | H | -.5317* |
| --- | H | Cl | $OCH_3$ | $OCH_3$ | H | -.5297 |
| --- | Cl | H | -O-$CH_2$-O- | | H | -.5328* |

* The bromo analogs are active in rats (121) or in humans (158). Molecular orbital calculations were performed by Johnson and Green (159).

# APPENDIX B

## DOSES OF BROMOMETHOXYAMPHETAMINES HAVING AN EFFECT ON THE CONDITIONED AVOIDANCE RESPONSE IN THE RAT

TABLE 2. DOSES OF BROMOMETHOXYAMPHETAMINES HAVING AN EFFECT ON THE CONDITIONED AVOIDANCE RESPONSE IN THE RAT




| Compound | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | ED (mg/kg) |
|---|---|---|---|---|---|---|
| 43a | Br | H | H | $OCH_3$ | H | Inact. |
| 43b | H | Br | $OCH_3$ | H | H | 9* |
| 43c | H | $OCH_3$ | Br | H | H | 7.5 |
| 43d | Br | H | $OCH_3$ | $OCH_3$ | H | Inact. |
| 43e | H | $OCH_3$ | Br | $OCH_3$ | H | 10 |
| 43f | $OCH_3$ | H | Br | $OCH_3$ | H | 2.5 |

Compound 43b had amphetamine-like stimulant properties.

# APPENDIX C

## RELATIVE INTENSITY OF FLUORESCENCE FOR BROMOMETHOXYAMPHETAMINE HYDROCHLORIDES

TABLE 3. RELATIVE INTENSITY OF FLUORESCENCE FOR BROMOMETHOXYAMPHETAMINE HYDROCHLORIDES

| Compound[a] | absorption/ emission | Relative Intensity of Fluorescence[b] |
|---|---|---|
| Amphetamine·HCl | 335/380 | 68 |
| | 350/400 | 68 |
| 43a | 300/335 | 13.7 |
| 43b | 285/345 | 42 |
| 43c | 285/340 | 540 |
| 43d | 285/340 | 81 |
| 43e | 310/395 | 89.5 |
| 43f | 285/345 | 34 |
| DOM·HCl | 295/340 | 4,000. |

[a] Refer to Appendix B for structures of compounds.

[b] For the detailed procedure see Antun, et al, (147).